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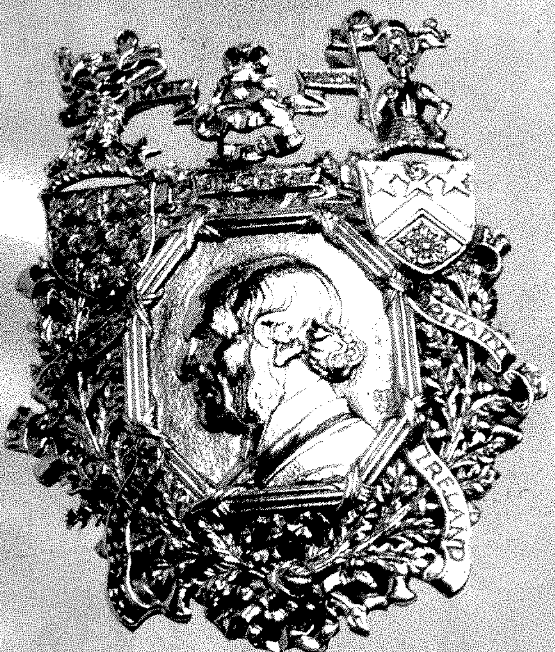

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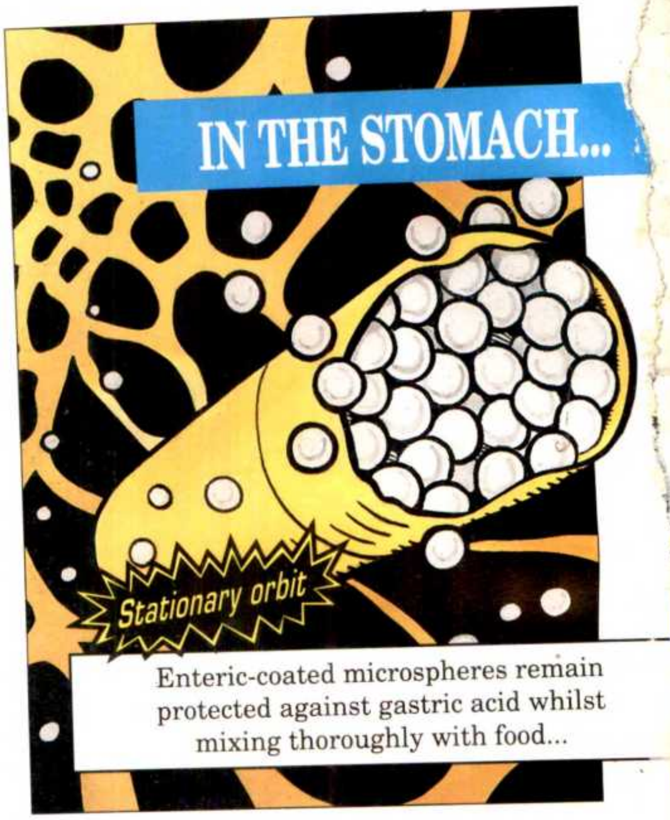
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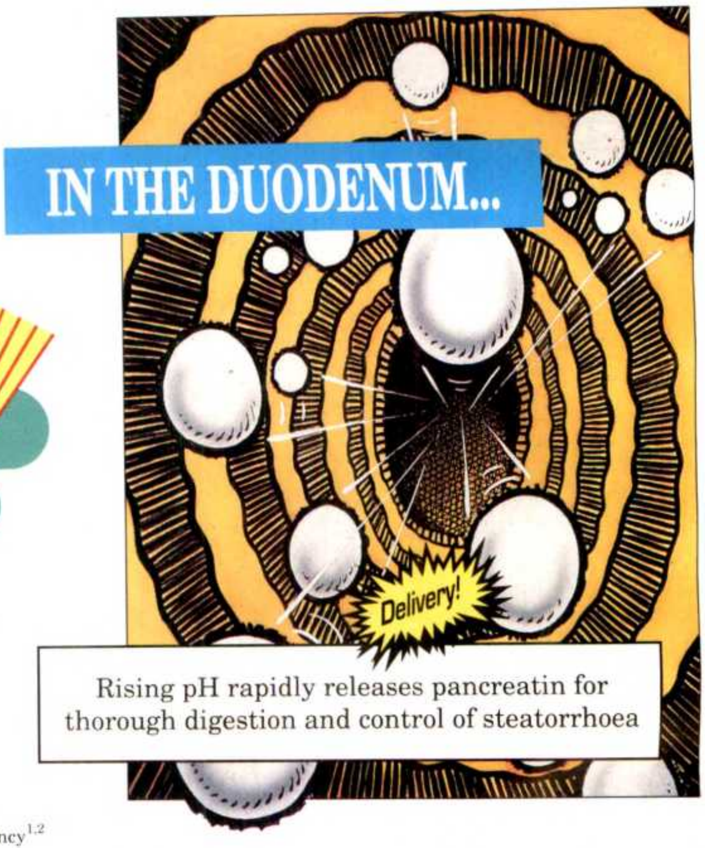
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References

1. Stead R J et al. *Thorax* 1987; **42**: 533-37
2. Beverley D W et al. *Arch Dis Child* 1987; **62**: 564-68

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References: 1. Bergqvist D. Post-operative thromboembolism. Frequency, etiology, prophylaxis. Berlin: Springer-Verlag, 1983. 2. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulm
embolism and venous thrombosis by perioperative administration of subcutaneous heparin. New Engl J Med 1988; 318:1162-1173. 3. Bergqvist D, Mätzsch T, Burmark U S et al. Low molecular weight he
given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. Br J Surg 1988; 75:888-891. 4. Eriksson B I, Kälebo P, Anthmyr B O et al. Prevention of Deep
Thrombosis and Pulmonary Embolism After Total Hip Replacement. J Bone Joint Surg 1991;73A (4):484-493.

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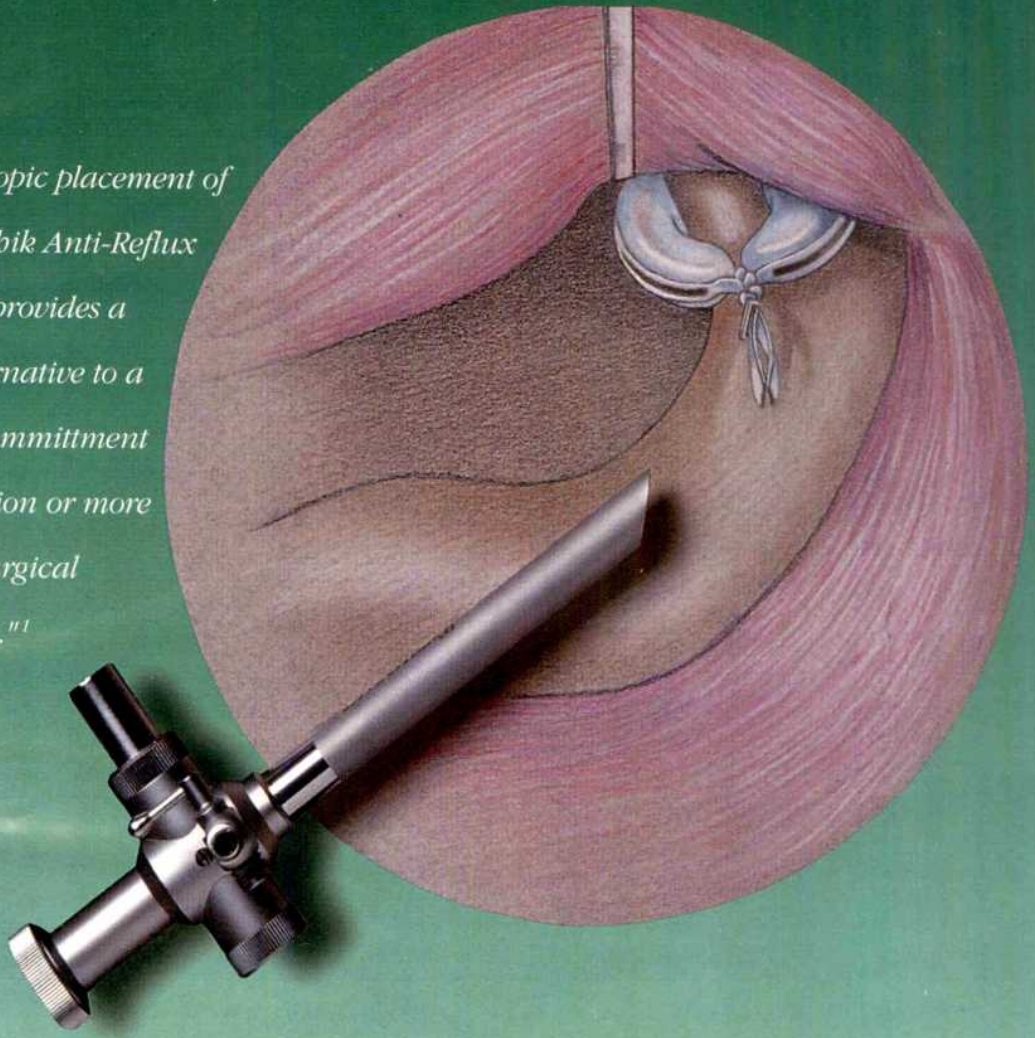

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[1] *MacPhee, W., "Laparoscopic Placement of the Angelchik Anti-Reflux Prosthesis." Submitted for presentation, 3rd World Congress of Endoscopic Surgery, Bordeaux, France, 1992.*

[2] *Angelchik, J.P.et al., "The Anti-Reflux Prosthesis: Simple, Effective Therapy for Gastroesophageal Reflux." Chapter 5 in* ***Debates in Clinical Surgery****, Volume 2, Simmons RL and AO Udekwa, eds., Mosby Year Book, St. Louis, 1991.*

[3] *Timoney, A.G. et.al., "The Angelchik Anti-Reflux Device: a 5-Year Experience"* ***Annals of Royal College of Surgeons of England****, 72: 185-187, 1990.*

[4] *Petterson,G.B., et.al., "The Dynamics of Lower Esophageal Sphincter Function"* ***Current Surgery****, 37: 143-145, 1980.*

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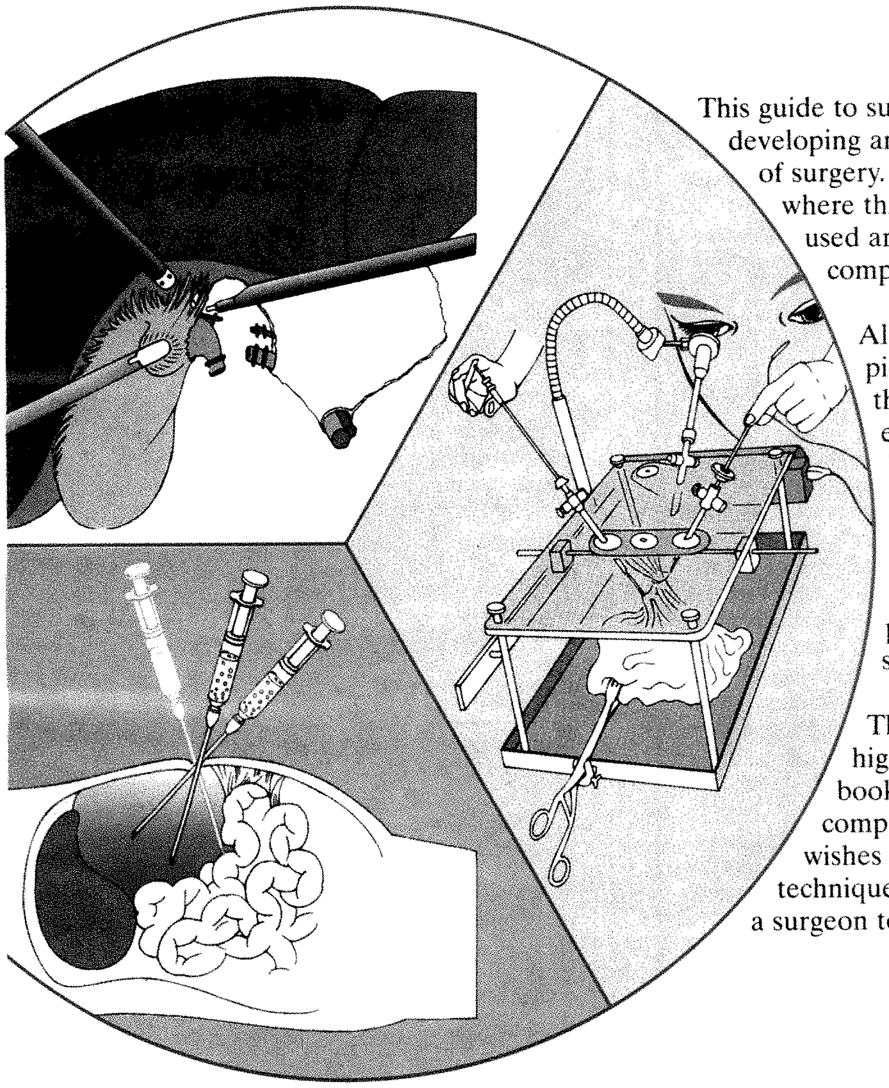

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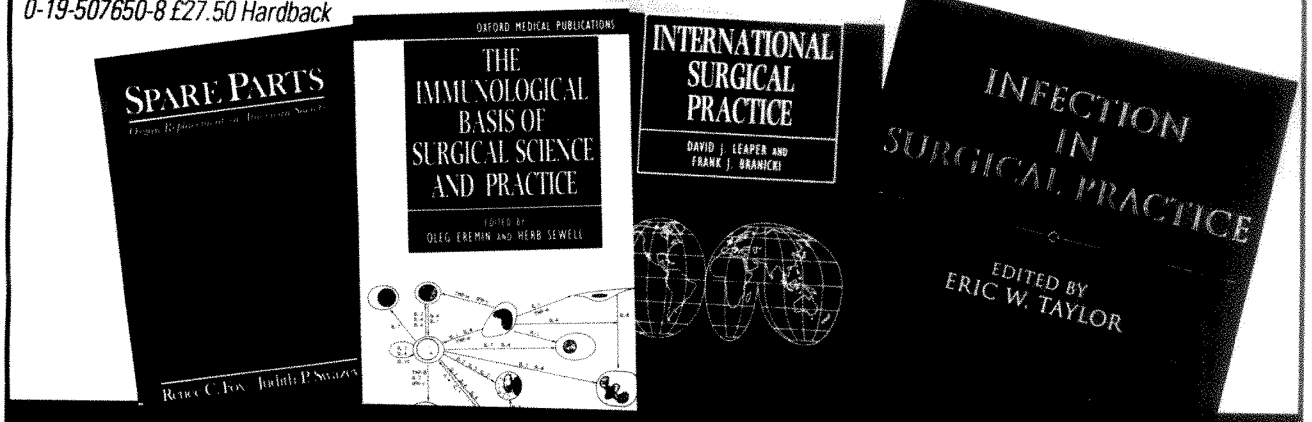

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Peter Lyon Harris (born 1944) is a consultant surgeon at Broadgreen Hospital, Liverpool (since 1979). Born and bred in Lancashire, he was educated at Manchester University and trained in Manchester before moving to Charing Cross Hospital as a senior registrar in 1974. His wide interests in vascular surgery embrace femoropopliteal vein grafting, aortic aneurysm surgery and thoracic outlet syndrome. Since 1990 he has been Secretary and Treasurer of the Vascular Surgical Society of Great Britain and Ireland.

Robin Williamson

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Congenital arteriovenous malformations

Abnormal communications between arteries and veins are responsible for arteriovenous malformations (AVMs). They are presumed to be present at birth although they are not always apparent. Usually they grow with age and, in women, may enlarge dramatically during puberty or pregnancy. Patients present because of disfigurement, pain, skin ulceration, haemorrhage or, rarely, heart failure. Important histological differences exist between capillary haemangiomas, which contain abundant mast cells, and other AVMs, in which mast cells are rare[1]. Haemangiomas are often not visible at birth, grow in the early months of life, tend to regress and, in 90 per cent of cases, involute naturally by the age of 5–10 years. They are not considered further here.

Syndromes such as Klippel–Trenaunay and Sturge–Weber are not as well defined as their names would suggest but are part of a widely overlapping spectrum. The clinical behaviour and prognosis of the remainder of AVMs are determined by the presence and quantity of shunting[2]. A simple hand-held Doppler ultrasonography probe may be used to examine the lesion. Patients with audible (or palpable) shunting who complain of pain, haemorrhage, skin ulceration or heart failure need urgent treatment. Angiography should be undertaken only when treatment is necessary and when embolization can be performed at the same session. Embolization is successful in reducing flow and improving symptoms in about 75 per cent of patients with significant shunting[3]. It may need to be repeated, but the indications for this are clinical deterioration or persistence of high-flow fistulas, which could compromise the heart. Embolization is particularly valuable in control of AVMs involving the pulmonary or central nervous system tissues; these are outside our experience.

Surgery is indicated for some malformations. Symptomatic, mainly venous, lesions with no arterial signal normally carry a better prognosis and can be investigated by plain radiography. This may reveal phleboliths, calcification, bony overgrowth or suspicious (possibly malignant) bone changes. Venography and duplex ultrasonography are sometimes indicated. Biopsy should be undertaken if doubt exists about the nature of any lesion that might be a sarcoma or vascular secondary tumour[4]. Superficial venous AVMs are best demonstrated by venous filling on dependence and by their venous signal using the hand-held Doppler ultrasonography probe. Small venous lesions can be excised and surgery offered to correct disfigurement or venous bleeding. Skin grafting may be needed to cover a large defect. It is important to balance the benefits of excision with the final appearance, and with the relatively benign clinical course associated with these lesions.

In a small proportion of cases an AVM is found to be traumatic: a forgotten injury may have led to an arteriovenous fistula. When there is strong suspicion of this from angiography, the lesion is usually best treated surgically if easily accessible.

In the past many AVMs were treated surgically by ligating the feeding vessels; this may still be appropriate in an immediately life-threatening situation. However, malformations may subsequently enlarge and access for embolization procedures has then been blocked. Appropriate treatment for these patients involves restoration of 'normal anatomy', either by direct reanastomosis of the feeding vessel or bypass grafting using vein or prosthetic material. This allows access for therapeutic embolization[5]. Ligation of feeding vessels should, as a rule, be avoided.

Excision of an unsightly, ulcerated or bleeding AVM may be desirable if embolization is not possible or make-up does not cover it. The extent of the malformation and the tissues involved must be assessed carefully. If the preoperative plain radiograph is normal, deep tissue involvement may best be excluded by non-invasive magnetic resonance imaging[6]. If muscle groups and nerves are involved, a decision must be made whether partial or complete excision is appropriate or possible. Excision may require the combined skills of plastic, orthopaedic and vascular surgeons. Large superficial highly vascular AVMs may be controlled by a technique described by Popescu[7]. Hand-held needles are used to under-run the tissue, returned

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through the dermis and tied, compressing the malformation. This 'mattress' effect leads to fibrosis and can help control the lesion.

Amputation is not often necessary. However, persistent skin ulceration or haemorrhage from a small highly vascular AVM of the finger or foot can be painful and distressing. Embolization might endanger the whole hand or foot; in selected cases amputation of a digit may actually preserve useful function. Major amputation is now rare, as embolization usually provides sufficient control of any large peripheral malformation. Nevertheless, the pelvic region remains an area of difficulty and potential danger; it is so well supplied with collaterals that embolization may fail. This may eventually lead to hindquarter amputation.

It is important that unnecessary angiography is not performed in low-flow AVMs and that in high-flow lesions embolization is planned to occur at the time of angiography. Surgery should be undertaken only when an AVM has been properly defined and symptoms justify an operation. While it is wrong to believe that AVMs are best treated by primary surgery, careful selection will enable up to 20 per cent of patients to be cured or their lesions well controlled by this means[8].

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1. Mulliken JB, Zetter BR, Folkman J. *In vitro* characterization of endothelium for hemangiomas and vascular malformations. *Surgery* 1982; **92**: 348–53.
2. Halliday AW, Mansfield AO. Arteriovenous malformations: current management approaches. *Br J Hosp Med* 1989; **42**: 196–202.
3. Hemingway AP, Smith EJ, Allison DJ. Embolisation in the treatment of systemic arteriovenous malformations: an analysis of 137 procedures. In: Silvestre ME, ed. *Radiology*. Amsterdam: Elsevier, 1987: 415–19.
4. Savader SJ, Savader BL, Otero RR. Intraosseous arteriovenous malformations mimicking malignant disease. *Acta Radiol* 1988; **29**: 109–14.
5. Strachan J, Hemingway AP, Mansfield AO, Allison DJ. Embolisation of an arteriovenous malformation following surgical reconstruction of a previously ligated lingual artery. *Journal of Interventional Radiology* 1986; **1**: 79–82.
6. Pearce WH, Rutherford RB, Whitehill TA, Davis K. Nuclear MRI: its diagnostic value in patients with congenital venous malformations of the limbs. *J Vasc Surg* 1988; **8**: 64–70.
7. Popescu V. Intratumoral ligation in the management of orofacial cavernous haemangiomas. *Journal of Maxillofacial Surgery* 1985; **13**: 99–107.
8. Halliday AW, Smith EJ, Jackson J, Allison DJ, Mansfield AO. Indications for surgery for arteriovenous malformations. *Br J Surg* 1992; **79**: 361–2.

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Perioperative nutritional support

Although malnutrition, a reduction in body reserves, compromises recovery and the capacity for healing following any surgical procedure[1], the risks are at their highest when major surgery includes intestinal anastomosis, an observation first noted[2] in 1936 and since confirmed by several investigators[1]. A period of up to 1 week with no oral intake generally poses few problems, provided fluid and electrolyte requirements are met. Any temporary gut dysfunction following surgery can usually be circumvented by the well established dogma of 'nasogastric suction and intravenous fluids'. However, there is an important minority of patients who are unable to ingest adequate nutrients for prolonged periods after surgery, and in these perioperative nutritional support is essential.

The support required will vary; in this context the concept of 'intestinal failure' is valuable. Intestinal failure is defined as a 'reduction in functioning gut mass below the minimal necessary for the adequate digestion and absorption of nutrients'[3]. In its broadest sense temporary intestinal failure after gastrointestinal surgery is practically inevitable, but it becomes a problem only with prolonged gut dysfunction. A successful outcome from any surgical intervention depends on a number of factors: the skill of the operator and the healing capacity of the patient are among the most important[1]. With specialization in surgery, many general surgeons are increasingly tending to become gastrointestinal specialists. All surgeons who resect portions of the gut, or who undertake major intra-abdominal surgery, occasionally encounter patients with prolonged gut dysfunction, and they can no longer ignore options for life-saving advances in artificial nutritional support. Nevertheless, recent evidence suggests that such support is unstructured, inappropriate and in many cases detrimental to patients in the majority of hospitals in the UK[4].

In broad terms, nutritional support involves a range of activities, extending from prescribing the oral intake of specialized (usually liquid) enteral feeds, providing access to the available functioning gut (in the form of enteral tubes and stomas), and bypassing the intestinal tract in patients with intestinal failure (in the form of total parenteral nutrition (TPN)). The traditional surgical interest in TPN has resulted in a relative neglect of the other methods. As in all aspects of medicine, the skill of clinical nutrition involves the two fundamental processes of informed decision making and institution of appropriate treatment. In this context, enteral feeding is the goal to strive for[5]. Sadly, in many patients who might be expected to need postoperative nutritional support, the surgeon fails to consider enteral access; the patient with a functioning but inaccessible gut who develops complications after surgery receives TPN when enteral access would allow safer, more effective, nutrition. The watershed between enteral and parenteral support should be determined by the presence or absence of intestinal failure[3], which is the only absolute indication for TPN. Despite technological advances, such nutrition still carries substantial complications. Many of these are catheter related; even in experienced hands, central venous catheter sepsis, displacement and mechanical problems occur in at least 10 per cent of cases[6]. At least a further 5 per cent of patients receiving TPN develop metabolic derangements.

The unbalanced emphasis placed on TPN is exemplified by a recent large multicentre trial. The objective of the Veterans' Affairs study was to define the role of preoperative and perioperative TPN in patients undergoing major gastrointestinal surgery[7]. The initial entry criteria for the study excluded 3 per cent of the overall sample who had an absolute requirement for TPN. Following randomization of more than 800 patients, approximately 5 per cent of the 395 given TPN were severely malnourished and appeared to derive benefit from such nutrition. In the remaining 95 per cent, who were less severely malnourished, TPN resulted in an increase in major complications, mainly infectious in nature, compared with controls. Not surprisingly, these data have been presented as suggesting that perioperative TPN has an unproven role and may be detrimental[7]. However, this is misleading, as patients with intestinal failure for whom TPN was vital were excluded. Furthermore, those with an intact functioning gut could have been more appropriately nourished with enteral nutrition. A realistic analysis of this study suggests that TPN is life-saving in patients with intestinal failure and improves the outcome in those who are severely malnourished. In borderline-to-severe malnutrition, the risks of TPN outweigh the benefits. In the light of these results, preoperative and perioperative enteral nutrition may prove beneficial but evaluation is awaited.

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What then are the essential aspects of perioperative nutrition for gastrointestinal surgeons? They should have a working knowledge of nutritional support and be able to identify patients for whom nutrition may represent an important limiting factor in recovery after operation. They should be aware of the recent advances in enteral feeding, particularly of fine-bore nasoenteral feeding tubes[5] and non-operative gastrostomy insertion[8]. Any surgeon who opens the abdomen should be capable of performing a gastrostomy or feeding jejunostomy in appropriate cases; when reoperating on patients for complications surgeons should bear in mind the possible need for enteral access. In this context the technique of needle-catheter jejunostomy as described by Delaney *et al.*[9] is to be recommended. With modern kits, a jejunostomy is quick and easy to perform, is associated with minimal complications and is easily removed if not required. The gastrointestinal surgeon should have a general understanding of the term and consequences of prolonged intestinal failure[3]. He or she should be aware that TPN is associated with mortality and substantial morbidity[6], but also that it is generally beneficial in patients with prolonged intestinal failure.

It would be impractical for all general surgeons to acquire detailed knowledge of all aspects of nutritional support: who then will decide which patients are likely to benefit from a particular perioperative nutritional intervention? Common sense helps[10], but a recent report from the King's Fund Centre has suggested that further awareness and training, and a multidisciplinary nutrition team approach to all aspects of nutritional support is required in all hospitals[4]. Surgeons have traditionally led the way in practical nutritional support and should continue to play their part. An understanding of perioperative nutritional needs should be an essential element of training for all who undertake major surgery, especially procedures on the gastrointestinal tract.

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1. Dempsey DT, Mullen JL, Buzby GP. The link between nutritional status and clinical outcome: can nutritional intervention modify it? *Am J Clin Nutr* 1988; **47**: 352–6.
2. Studley HO. Percentage of body weight loss: a basic indicator of surgical risk in patients with chronic peptic ulcer. *JAMA* 1936; **106**: 458–60.
3. Fleming CR, Remington M. Intestinal failure. In: Hill GL, ed. *Nutrition and the Surgical Patient.* Edinburgh: Churchill Livingstone, 1981: 219–35.
4. King's Fund Centre. *A Positive Approach to Nutrition as Treatment.* London: King's Fund Centre: 1992.
5. Payne-James J, Silk DBA. Enteral nutrition: background, indications and management. *Baillieres Clin Gastroenterol* 1988; **2**: 815–47.
6. Mughal MM. Complications of central venous catheters. *Br J Surg* 1989; **76**: 15–21.
7. Veterans' Affairs Total Parenteral Nutrition Cooperative Study Group. Perioperative total parenteral nutrition in surgical patients. *N Engl J Med* 1991; **325**: 525–32.
8. Moran BJ, Taylor MB, Johnson CD. Percutaneous endoscopic gastrostomy. *Br J Surg* 1990; **77**: 858–62.
9. Delaney HM, Carnevale NJ, Garvey JW. Jejunostomy by a needle catheter technique. *Surgery* 1973; **73**: 786–90.
10. Hill GL. Surgical nutrition: time for some clinical common sense. *Br J Surg* 1988; **75**: 729–30.

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Medullary thyroid carcinoma

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Medullary thyroid carcinoma accounts for 5–10 per cent of thyroid malignancies and occurs sporadically, and in three familial settings with autosomal dominant inheritance. Calcitonin, a 32 amino acid 3·5-kDa protein, is a biochemical marker of the tumour. Serum levels correlate with disease burden. Treatment initiated by screening allows disease removal at a premalignant phase: C cell hyperplasia. Genetic linkage studies locate the multiple endocrine neoplasia type 2A gene near the centromere of chromosome 10. Flanking genetic markers may allow polymorphic probes to examine DNA from a once-only blood sample to identify affected individuals. At what age thyroidectomy should be carried out in these patients is unclear.

Medullary thyroid carcinoma (MTC), recognized[1] since 1959, constitutes 5–10 per cent of all thyroid malignancies. It occurs within three familial syndromes and as a sporadic disease.

Classification

The multiple endocrine neoplasia (MEN) syndrome described by Sipple in 1961 (MEN 2A) consists of an association between MTC, phaeochromocytoma and hyperparathyroidism, and is inherited as an autosomal dominant condition with complete penetrance and variable expressivity[2]. MTC develops in all affected members and is usually detectable by the second decade of life, although a palpable thyroid nodule may not become clinically evident until the age of 40 years. The tumour has a variable prognosis in these families, usually demonstrating slow growth; rapid progression may, however, occur..

MTC in families with MEN 2B is a more aggressive disease (5-year survival rate <35 per cent)[3] and may develop before the age of 12 months. The syndrome is characterized by MTC, phaeochromocytoma, the striking appearance of marfanoid habitus and multiple mucosal neuromas affecting the lips, eyelids, tongue and oropharynx with ganglioneuromas of the gastrointestinal tract that may predispose to bowel motility disorders.

Familial non-MEN MTC was described recently as an autosomal dominant condition with no associated endocrinopathies[4]. The disease is more indolent, with a mean age at presentation of 45 years and an excellent 5-year survival rate.

Sporadic MTC presents as a palpable mass in the neck during the fifth or sixth decade of life. Only one thyroid lobe is affected, local metastases are frequently found at the time of surgery, and recurrence is common. However, the disease is less aggressive than MTC in MEN 2B, with a 70 per cent 7-year survival rate reported[5].

Pathology

MTC develops in parafollicular C cells derived from the neural crest, located in the upper and middle portions of the thyroid gland. It occurs as a unilateral focus in the sporadic disease but is multicentric in hereditary MTC, involving both lobes in almost all patients. The tumour has a gross appearance of grey/white or tan nodules with a gritty texture and areas of haemorrhage, necrosis, fibrosis or calcification. Histologically it consists of uniform polygonal or spindle-shaped cells within a variable fibrous stroma that may often contain amyloid, particularly in larger tumours. C cell hyperplasia is found in the gland in patients with familial syndromes but not in sporadic MTC[5]. The tumour may be identified by light microscopy but immunohistochemical staining for calcitonin is required to detect C cell hyperplasia.

Biochemistry

Calcitonin, a 32 amino acid 3·5-kDa protein, is secreted by thyroid C cells and serves as an excellent tumour marker, although its precise physiological role is not known. In animals, calcitonin has a calcium-lowering action by inhibition of osteoclastic bone resorption. In humans it plays a minor role in calcium homoeostasis – thyroidectomy has little effect on serum calcium levels. Calcitonin has therapeutic application in the treatment of Paget's disease and hypercalcaemia.

MTC messenger RNA has been used to derive complementary DNA, from which the structure of the calcitonin precursor has been predicted[6]. The calcitonin gene is flanked by the *C*-terminal peptide PDN21 and a larger *N*-terminal peptide. Calcitonin and PDN21 are coexpressed in C cells, probably as a result of post-translational cleavage of the two peptides from the same precursor molecule[7]. MTC is capable of producing other hormones such as adrenocorticotrophic hormone, bombesin, somatostatin, 5-hydroxytryptamine, prostaglandins, carcinoembryonic antigen (CEA), substance P and vasoactive intestinal peptide with no clinical significance; Cushing's syndrome has, however, been reported[8]. Immunohistochemical markers for MTC include calcitonin, histaminase (not present in normal C cells or C cell hyperplasia), dopamine decarboxylase (present in normal cells but greatly increased in areas of MTC), neurone-specific enolase and the acidic protein chromogranin[9,10].

Diagnosis

Patients with palpable MTC may present with single or multiple nodules, advanced local disease (cough, hoarseness, dysphagia and cervical lymphadenopathy) or with signs of metastatic disease in lung, liver or bone. Occasionally patients develop diarrhoea owing to high levels of calcitonin stimulating intestinal secretion of water and electrolytes.

Radiology

Characteristic irregular dense calcification may occur, particularly in longstanding tumours. Ultrasonography detects tumours as small as 4 mm and has limited application in the detection of recurrent disease[11]. Primary tumours and metastases may be localized using radioisotope techniques where available; pentavalent ^{99m}Tc-dimercaptosuccinic acid is considered superior to standard technetium, ^{131}I, or ^{131}I-*m*-iodobenzylguanidine radioisotope scans[12,13].

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Biopsy

Fine-needle aspiration cytology may be diagnostic; MTC smears show a predominance of spindle cells and the presence of a substance with amyloid staining properties.

Serum markers

Basal or stimulated calcitonin levels are raised in virtually all patients with MTC. The calcitonin radioimmunoassay, developed in 1970, has proved an invaluable screening test for the detection of preclinical disease and early tumour recurrence after surgery in MEN 2 family members[14]. The normal range for the radioimmunoassay varies between laboratories but usually lies below 300 pg/ml. In patients with a palpable tumour this may rise to >1000 pg/ml and in those with metastatic disease to >100 000 pg/ml. Calcium and pentagastrin are potent secretagogues for calcitonin and the combined administration of calcium gluconate (2 mg/kg) and pentagastrin (0·5 μg/kg) provides a synergistic increase in calcitonin level detected by peripheral blood sampling at 0, 1, 2, 3, 5 and 10 min after completion of injection. Most people experience mild side-effects of flushing, sweating and a sensation of retrosternal, epigastric or pharyngeal pressure. Occasionally more severe symptoms and weakness occur; fewer than 1 per cent of patients experience hypotension, cardiac arrhythmia and prostration[15] for 24–48 h.

Treatment

All patients with MTC require total thyroidectomy with meticulous removal of all thyroid tissue and preservation of the parathyroid glands and recurrent laryngeal nerves. Although 80 per cent of patients with sporadic MTC have unilateral disease, each patient should be regarded as a potential new index case for a familial syndrome. Chances of cure are optimized by careful primary surgery including prophylactic central lymph node dissection from the hyoid to the innominate vessels, extending out to the internal jugular veins, because 50 per cent of patients present with nodal metastases[16]. Routine radical neck dissection is not necessary in every case but lateral neck dissection is performed when cervical metastases are apparent[5].

Phaeochromocytoma should be excluded by preoperative investigations in patients with MEN 2A or 2B, and adrenalectomy undertaken if required 2 weeks before thyroidectomy to prevent adrenergic crisis. Patients with MEN 2A should be screened for hyperparathyroidism by testing serum calcium and parathyroid hormone levels. In contrast to MEN 1, selective removal of only grossly enlarged glands can be performed in patients with MEN 2A without risk of recurrent hypercalcaemia[17]. Total parathyroidectomy with parathyroid autotransplantation is indicated only in patients with MEN 2A who have hypercalcaemia and enlargement of all four parathyroid glands.

Prognostic indicators

Stage

The method of investigation and type of MTC influence the stage at diagnosis[18]. Some 64 per cent of patients with sporadic MTC, 60 per cent with MEN 2B, and 26 per cent with MEN 2A had extrathyroid disease at primary surgery in one study[16]. Of patients with palpable tumours, 41 per cent had local node involvement, while 14 per cent of those detected by raised basal calcitonin concentrations and none of those with normal basal but raised stimulated calcitonin levels had metastatic disease[16].

Calcitonin level

The preoperative stimulated calcitonin level correlates with tumour weight or extent of disease and regional spread. Residual disease after surgery, distant metastases and death occur more commonly in patients with a preoperative calcitonin concentration[18–20] >10 000 pg/ml. In the familial syndromes, where MTC is diagnosed by calcitonin level rather than clinically, patients with a stimulated level <1000 pg/ml have a 95 per cent chance of cure; this falls to 40 per cent with a level[8] >10000 pg/ml.

The calcitonin concentration doubling time has been suggested as a better prognostic indicator than preoperative or postoperative assay[20]. Tumour growth, which influences survival rate, is defined by the initial or residual tumour volume after surgery and the tumour doubling time. The residual tumour weight may be derived from the calcitonin level and measurement of the time to doubling of the latter may allow estimation of the expected duration of survival following surgery.

Immunohistochemistry

Tumours that stain homogeneously for calcitonin using immunoperoxidase techniques carry an excellent prognosis compared with those with heterogeneously staining MTC cells, which behave aggressively and carry a poor prognosis[21,22].

Carcinoembryonic antigen

CEA has been demonstrated immunohistochemically in MTC tissue, and raised plasma concentrations are occasionally found in patients with a high tumour burden who progress to metastatic disease without a parallel rise in calcitonin level[23,24]. In early MTC, CEA and calcitonin are coexpressed in all cells, but in disseminated MTC an inverse relationship has been demonstrated between CEA and calcitonin staining: cells that stain poorly for calcitonin have large amounts of CEA and vice versa. This suggests that serial CEA measurements in addition to calcitonin levels may be important in some patients[25].

Persistent hypercalcitoninaemia

Stimulated calcitonin assays are performed 1 month after operation and, if normal, at annual intervals thereafter. If raised, levels are remeasured at 3 and 6 months. Elevations in plasma calcitonin concentration can occur without the site of recurrence being clinically obvious. The tumour may be indolent in its rate of growth and progression and so it must be shown that the effort of localization and repeat intervention is likely to be worth while. A reduction in calcitonin level may occur following removal of micrometastases at reoperation, but is seen most commonly in patients with sporadic MTC who have unilateral disease. Selective venous catheterization is not essential in these patients because recurrence will be on the same side as the primary lesion and unilateral modified radical neck dissection may be successful[26].

In patients with bilateral disease, cervical lymph node metastases may be localized by venous blood sampling from the jugular, innominate and right hepatic veins after femoral vein catheterization. For selective:peripheral calcitonin gradients >2·5, histological confirmation of localization should be achieved in all cases; confirmation may be disappointing below this level[27]. Histological verification of biochemically determined recurrence may not be obtained for several reasons: slowly growing microscopic foci may be undetectable and distortion of the cervical anatomy from previous surgery or radiotherapy may obscure dissection. Reoperation may not be indicated in patients with stable metastatic disease. Although previous reoperation and radiotherapy reduce the chances of biochemical cure, this may still occur in up to 30–40 per cent of cases following meticulous microdissection of the superior mediastinum and both sides of the neck[28].

MTC may metastasize early to the liver and may be detected by hepatic arteriography. Venous sampling of calcitonin in peripheral and hepatic veins and the superior and inferior vena cava may localize hepatic metastases that are undetectable by conventional clinical and radiological investigation. A raised stimulated calcitonin level within 5 min of injection in the hepatic vein compared with levels in the inferior cava or peripherally is diagnostic. Normalization of the calcitonin level is unlikely to be achieved in the majority of patients with persistent hypercalcitoninaemia, and radical resection of recurrent disease does not have proven long-term survival benefit[26,29].

Metastatic medullary thyroid carcinoma

The treatment of metastatic disease has been disappointing. Radiotherapy has been associated with tumour regression and prolonged survival in some cases[30], but the high incidence of complications such as radiation tracheitis and cervical fibrosis has restricted its use to patients with inoperable MTC and locally advanced or metastatic disease. Partial regression with doxorubicin has been reported in one series but not confirmed[31]. Methotrexate, 5-fluorouracil, cisplatin and carmustine have not shown benefit[32]. MTC cells do not concentrate iodine and so ^{131}I is of no benefit if total thyroidectomy has been performed[33,34].

Screening

Up to 20 per cent of patients presenting with apparently sporadic MTC are ultimately found to have relatives with C cell disease (hyperplasia or MTC)[15]. All first-degree relatives over 1 year old should be screened by clinical examination and measurement of basal calcitonin levels, because patients with screen-detected disease have a good prognosis. The calcium–pentagastrin-stimulated calcitonin test is generally reserved for adults because the discomfort produced in children is unlikely to be justified[35].

In at-risk patients, a basal calcitonin concentration <200 pg/ml and stimulated level >1000 pg/ml (fivefold rise) is an indication for surgery. Relatives with stimulated calcitonin levels between 300 and 1000 pg/ml are observed and the assay repeated in 6 months. If persistent, the situation may be clarified by inferior thyroid vein catheterization and sampling of stimulated calcitonin[36]. Patients with no clinical evidence of disease, normal basal and raised stimulated calcitonin levels are diagnosed at a younger age, have smaller primary tumours and a lower incidence of regional metastases and residual disease[18]. Difficulties may arise with interpretation of assay results, for example in patients with a high basal calcitonin level but no significant rise on stimulation, a normal basal level with a less than twofold rise following stimulation, and those with a raised basal or stimulated calcitonin level that falls to normal over a short period of time[15]. The calcitonin concentration in sera stored at −20°C may fall to a misleadingly low value after 4 weeks, and false-positive calcitonin level elevation occurs in pregnancy, thyroiditis, hypothyroidism and hyperthyroidism, as well as in other malignancies[15].

The stimulated calcitonin assay detects over 90 per cent of carriers[37] by the age of 30 years, but many years of repeated sampling may be required before the children of an affected parent can be excluded from risk. In 1987 the gene for MEN 2A was mapped by genetic linkage[38,39] to a locus near the centromere of chromosome 10. It is hoped that the use of DNA markers around the MEN 2A locus may overcome some of the limitations of the biochemical screening test. The interstitial retinol-binding protein gene (*RBP3*) and DNA segments recognized by the MCK2 and TB14.34 probes are tightly linked to the gene for susceptibility to MEN 2A. Using a set of these polymorphic probes to examine DNA obtained from a single blood sample, it has proven possible to distinguish between the two versions of chromosome 10 of an affected parent, deduce which is carrying the susceptibility gene, and establish whether this has been passed on to an at-risk child. DNA marker analysis assumes that the chromosome location of the mutation responsible for MEN 2A is identical in all affected families[40]. Genetic screening has significant advantages: the test need be performed only once and further pentagastrin testing may be performed less frequently than once a year, or even discontinued, in those relatives with low-risk estimates. A difficulty arises, however, in recommending thyroidectomy to patients who have genetic markers of susceptibility but normal stimulated calcitonin levels. Linkage studies using DNA markers at present show a 3 per cent risk of misdiagnosis and require the participation of many family members[40,41]. However, in combination with measurement of stimulated calcitonin level they will continue to provide a reliable screening method until the specific genetic abnormality in MEN 2A is characterized.

References

1. Hazard JB, Hawk WA, Crile G. Medullary (solid) carcinoma of the thyroid – a clinicopathologic entity. *J Clin Endocrinol Metab* 1959; **19**: 152–61.
2. Sipple JH. The association of pheochromocytoma with carcinoma of the thyroid gland. *Am J Med* 1961; **31**: 163–6.
3. Carney JA, Sizemore GW, Hayles AB. C-cell disease of the thyroid gland in multiple endocrine neoplasia type 2b. *Cancer* 1979; **44**: 2173–83.
4. Farndon JR, Leight GS, Dilley WG *et al.* Familial medullary carcinoma without associated endocrinopathies: a distinct clinical entity. *Br J Surg* 1986; **73**: 278–81.
5. Brunt LM, Wells SA Jr. Advances in the diagnosis and treatment of medullary thyroid carcinoma. *Surg Clin North Am* 1987; **67**: 263–79.
6. Craig RK, Hall L, Edbrooke MR *et al.* Partial nucleotide sequence of human calcitonin precursor mRNA identifies flanking cryptic peptides. *Nature* 1982; **295**: 345–7.
7. Sikri KL, Varndell IM, Hamid QA *et al.* Medullary carcinoma of the thyroid. An immunocytochemical and histochemical study of 25 cases using eight separate markers. *Cancer* 1985; **56**: 2481–91.
8. Wells SA Jr, Dilley WG, Farndon JR *et al.* Early diagnosis and treatment of medullary thyroid carcinoma. *Arch Intern Med* 1985; **145**: 1248–52.
9. Baylin SB, Beaven MA, Engelman K *et al.* Elevated histaminase activity in medullary carcinoma of the thyroid gland. *N Engl J Med* 1970; **283**: 1239–44.
10. Atkins FL, Beaven MA, Keiser HR. Dopa decarboxylase in medullary carcinoma of the thyroid. *N Engl J Med* 1973; **289**: 545–8.
11. Schwerk WB, Grun R, Wahl R. Ultrasound diagnosis of C-cell carcinoma of the thyroid. *Cancer* 1983; **55**: 624–30.
12. Ohta H, Yamamoto K, Endo K *et al.* A new imaging agent for medullary carcinoma of the thyroid. *J Nucl Med* 1984; **25**: 323–5.
13. Udelsman R, Mojiminiyi OA, Soper NDW *et al.* Medullary carcinoma of the thyroid: management of persistent hypercalcitoninaemia utilizing (^{99m}Tc)(v) dimercaptosuccinic acid scintigraphy. *Br J Surg* 1989; **76**: 1278–81.
14. Tashjian AH, Howland BG, Melvin KEW *et al.* Immunoassay of human calcitonin: clinical measurement, relation to serum calcium and studies in patients with medullary carcinoma. *N Engl J Med* 1970; **283**: 890–5.
15. Simpson WJ, Carruthers JS, Malkin D. Results of a screening program for C-cell disease (medullary thyroid cancer and C-cell hyperplasia). *Cancer* 1990; **65**: 1570–6.
16. Russell CF, Van Heerden JA, Sizemore GW *et al.* The surgical management of medullary thyroid carcinoma. *Ann Surg* 1983; **197**: 42–8.
17. Block MA, Jackson CE, Tashjian AH. Management of parathyroid glands in surgery for medullary thyroid carcinoma. *Arch Surg* 1975; **110**: 617–24.
18. Wells SA Jr, Baylin SB, Gann DS. Medullary thyroid carcinoma: relationship of method of diagnosis to pathologic staging. *Ann Surg* 1978; **188**: 377–83.
19. Wells SA Jr, Baylin SB, Leight GS *et al.* The importance of early diagnosis in patients with hereditary medullary thyroid carcinoma. *Ann Surg* 1982; **195**: 595–9.
20. Miyauchi A, Matsuzuka F, Kuma K *et al.* Evaluation of surgical results and prediction of prognosis in patients with medullary thyroid carcinoma by analysis of serum calcitonin levels. *World J Surg* 1988; **12**: 610–15.
21. Lippman SM, Mendelsohn G, Trump DL *et al.* The prognostic and biological significance of cellular heterogeneity in medullary thyroid carcinoma: a study of calcitonin, L-dopa decarboxylase and histaminase. *J Clin Endocrinol Metab* 1982; **54**: 233–40.
22. Saad MF, Ordonez NG, Guido JJ *et al.* The prognostic value

of calcitonin immunostaining in medullary carcinoma of the thyroid. *J Clin Endocrinol Metab* 1984; **59**: 850–6.
23. Busnardo B, Girelli ME, Simioni N *et al.* Nonparallel patterns of calcitonin and carcinoembryonic antigen levels in the follow-up of medullary thyroid carcinoma. *Cancer* 1984; **53**: 278–85.
24. Rougier P, Calmettes C, LaPlanche A *et al.* The values of calcitonin and carcinoembryonic antigen in the treatment and management of nonfamilial medullary thyroid carcinoma. *Cancer* 1983; **51**: 855–62.
25. Mendelsohn G, Wells SA Jr, Baylin SB. Relationship of tissue carcinoembryonic antigen and calcitonin to tumor virulence in medullary thyroid carcinoma. *Cancer* 1984; **54**: 657–62.
26. Norton JA, Doppman JL, Brennan MF. Localization and resection of clinically inapparent medullary carcinoma of the thyroid. *Surgery* 1980; **87**: 616–22.
27. Mrad MDB, Gardet P, Roche A *et al.* Value of venous catheterization and calcitonin studies in the treatment and management of clinically inapparent medullary thyroid carcinoma. *Cancer* 1989; **63**: 133–8.
28. Tisell LE, Hansson G, Jansson S *et al.* Reoperation in the treatment of asymptomatic metastasizing medullary thyroid carcinoma. *Surgery* 1986; **99**: 60–6.
29. Block MA, Jackson CE, Tashjian AH. Management of occult medullary thyroid carcinoma. *Arch Surg* 1978; **113**: 368–72.
30. Steinfeld AD. The role of radiation therapy in medullary thyroid carcinoma. *Radiology* 1977; **123**: 745–5.
31. Gottlieb JA, Hill CS. Chemotherapy of thyroid cancer with Adriamycin. *N Engl J Med* 1974; **290**: 193–7.
32. Cance WG, Wells SA Jr. Multiple endocrine neoplasia type IIa. *Curr Probl Surg* 1985; **22**: 1–56.
33. Nieuwenhuijzen-Kruseman AC, Bussemaker JK, Frolic M. Radioiodine in the treatment of hereditary medullary carcinoma of the thyroid. *J Clin Endocrinol Metab* 1984; **59**: 491.
34. Saad MF, Guido JJ, Samaan NA. Radioactive iodine in the treatment of medullary carcinoma of the thyroid. *J Clin Endocrinol Metab* 1983; **57**: 124–7.
35. Hennessy JF, Wells SA, Ontjes DA *et al.* A comparison of pentagastrin injection and calcium infusion as provocative agents for the detection of medullary carcinoma of the thyroid. *J Clin Endocrinol Metab* 1974; **39**: 487–95.
36. Wells SA Jr, Baylin SB, Johnsrude IS *et al.* Thyroid venous catheterization in the early diagnosis of familial medullary thyroid carcinoma. *Ann Surg* 1982; **196**: 505–11.
37. Ponder BAJ, Ponder MA, Coffey R *et al.* Risk estimation and screening in families of patients with medullary thyroid carcinoma. *Lancet* 1988; **i**: 397–400.
38. Mathew CGP, Chin KS, Easton DF *et al.* A linked genetic marker for multiple endocrine neoplasia type 2a on chromosome 10. *Nature* 1987; **328**: 527–8.
39. Simpson NE, Kidd KK, Goodfellow PN *et al.* Assignment of multiple endocrine neoplasia type 2A to chromosome 10 by linkage. *Nature* 1987; **328**: 528–30.
40. Sobol H, Narod SA, Nakamura Y *et al.* Screening for multiple endocrine neoplasia type 2a with DNA-polymorphism analysis. *N Engl J Med* 1989; **321**: 996–1001.
41. Telenius H, Mathew CGP, Nakamura Y *et al.* Application of linked DNA markers to screening families with multiple endocrine neoplasia type 2A. *Eur J Surg Oncol* 1990; **16**: 134–40.

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Role of the neutrophil in adult respiratory distress syndrome

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Adult respiratory distress syndrome (ARDS) remains a significant cause of morbidity and mortality in surgical practice. Despite the continued advance of surgical technique and therapy, the mainstay of treatment of ARDS remains supportive. In the past decade cytokines have been found to be primary chemical mediators of the host response to inflammatory disease. The polymorphonuclear leucocyte has also emerged as a possible cellular mediator of the end-organ damage that characterizes these inflammatory processes. The role of the neutrophil as the primary cellular mediator of alveolar capillary membrane injury in ARDS remains controversial. This article reviews the relevant current literature and considers the implications of the prevailing evidence on future management of this syndrome.

Adult respiratory distress syndrome (ARDS) is one of the most feared complications in surgical practice and, despite advances in intensive care, its associated mortality rate remains around 60 per cent[1–3]. In particular, ARDS in patients with sepsis remains difficult to treat, even with the application of new generations of antimicrobial drugs. In the past decade understanding of the pathophysiology of this condition has expanded enormously and a new approach to treatment has evolved, that of 'biological response modification'. The genesis of this type of therapy relied on the realization that the fundamental pathophysiological event in ARDS is self-induced tissue injury: the host's own immune system mediates alveolar capillary membrane damage. Current therapeutic studies are aimed at modifying or inhibiting critical aspects of the inflammatory response to reduce the lung injury.

It is of interest that the aetiology of ARDS is so disparate and multifactorial, yet the pathological end-organ injury is remarkably singular[4,5]. The trigger that initiates a change in the immune system from defence to self-destruction and the immune components that are the primary cellular and humoral mediators in this process remain unknown and are the focus of ongoing research. This paper addresses the question of cellular mediators and, in particular, whether or not the neutrophil is implicated in the development of ARDS.

Neutrophil cytotoxicity

The neutrophil is undoubtedly capable of mediating the type of injury required to produce ARDS[6–8]. As a first line in cellular defence under normal conditions, neutrophils seek out and destroy invading organisms by using antimicrobial mechanisms tailored to the invader and its environment. The neutrophil armamentarium is conventionally divided into two types[7] according to location within the cell: membrane-associated systems generate reactive oxygen metabolites and a cytosolic system of intracellular granules contains proteinases and other enzymes.

Within the cell membrane, the enzyme reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase[9–11] shuttles electrons from cytosolic NADPH to molecular oxygen within the extracellular fluid, catalysing the reaction:

$$2O_2 + \mathrm{NADPH} \xrightarrow{\text{NADPH oxidase}} 2O_2^- + \mathrm{NADP}^+ + \mathrm{H}^+$$

This reaction generates two molecules of the superoxide radical (O_2^-). Although able to react with biological substrates[12], superoxide radicals preferentially interact at physiological pH in a dismutase reaction to form a molecule of hydrogen peroxide:

$$2O_2^- + 2\mathrm{H}^+ \xrightarrow{\text{superoxide dismutase}} \mathrm{H_2O_2} + O_2$$

Although hydrogen peroxide is also able to react with biological substrates[13,14], much of it is channelled into the production of a long-lived oxidant, hypochlorous acid (HOCl)[15,16].

$$\mathrm{H_2O_2} + \mathrm{Cl}^- + \mathrm{H}^+ \xrightarrow{\text{myeloperoxidase}} \mathrm{HOCl} + \mathrm{H_2O}$$

This reaction requires the enzyme myeloperoxidase[17], released from the cytosolic neutrophilic granules, to provide a link between the two arms of the neutrophil armamentarium. The long- and short-lived oxygen radicals formed by these reactions are unstable and extremely reactive; they are capable of disrupting the lipid membranes of neighbouring cells by peroxidation. They prevent normal actin metabolism within the cell cytoplasm[13] by altering cellular adenosine 5'-triphosphate (ATP) and calcium levels, resulting in changes in endothelial cell shape and hence a capillary leak typical of ARDS. In addition, oxygen radicals induce damage to cellular DNA[8]. This results in consumption of NAD to maintain DNA levels. NAD is therefore channelled away from synthesis of the NADP–NADPH system, with catastrophic consequences for cellular metabolism, in particular ATP production and the maintenance of reduced glutathione pools.

The cytosolic system of neutrophil granules contains a large family of proteolytic enzymes, bactericidal proteins, lysozyme and lactoferrin[18,19]. Proteolytic enzymes, in particular elastase, gelatinase and collagenase, have the potential to degrade much of the local host environment, which consists of collagen, elastin and basement membrane. Destruction of all or part of these connective tissue elements is characteristic of advanced lung injury in ARDS[20,21]. In the usual sequence of events during a typical acute inflammatory response, the local action of circulating antiproteinases[22,23] limits the destructive potential of the neutrophil to within phagocytic vacuoles. Similarly, during the normal response to pathogens, the destructive potential of neutrophil-generated reactive oxygen metabolites is limited by oxidant scavengers, such as superoxide dismutase

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and catalase[24], which are present in both the circulation and endothelial cells. It is of interest that circulating mature neutrophils are unable to manufacture elastin[25]; they merely store this enzyme in granules. Neutrophils, however, do express the gene for α_1-antitrypsin and are able to translate and secrete this protein in response to activation[26]. The neutrophil therefore provides in a limited way its own autoregulation against host injury. Furthermore, there exists a paradoxical interaction between neutrophil oxidant and the proteinase systems. Oxidants are able to inactivate proteinase inhibitors while activating other proteinases[27,28], therefore enhancing the destructive potential of the neutrophil. There thus exists a delicate balance between local tissue destruction and protection that, when disturbed, may result in the development of widespread injury.

Neutrophil physiology

The concept of neutrophil-mediated tissue injury is not new. In 1887, Metchnikoff[29] performed seminal observations on the comparative pathology of inflammation; since then, the neutrophil has been implicated as responsible for many inflammatory conditions. Knowledge of normal neutrophil physiology is essential to understanding how this cell participates in the pathophysiology of sepsis. In 1910, Andrews[30] speculated that:

> 'If the bone marrow is the birthplace of the neutrophil and the spleen is their ultimate tomb, while the blood is their means of transit, the lungs may serve as a weekend retreat where they may recuperate their energies'.

This illustrates two fundamental aspects of normal neutrophil kinetics. First, the cells exist at equilibrium in three separate pools: bone marrow, intravascular and interstitial[31]. Second, the pulmonary vascular bed is a major neutrophil reservoir, storing between 50 and 60 per cent of the total intravascular pool[32].

Neutrophil kinetics

The accumulation of neutrophils in normal lung vasculature and the vulnerability of the alveolar capillary membrane to injury under conditions of inflammatory stress seem more than coincidental. Neutrophils located in this pulmonary reservoir were thought to exist 'marginating' or rolling along vessel walls as a result of weak attractive forces and particle flow characteristics[33,34]. This marginating phenomenon has been demonstrated in postcapillary venules in systemic vascular beds[35]; however, recent evidence[36] suggests that the pulmonary circulation is unique in this respect, in that the majority of neutrophils in the lung are found in capillaries. Lien *et al.*[37] elegantly demonstrated, by videomicroscopy of the subpleural pulmonary circulation in dogs, that neutrophils were exclusively held up in the capillary beds and not in the postcapillary venules. Hogg[38] suggested that the anatomy of the pulmonary circulation and its low-pressure circuit are responsible for this capillary retention. The estimated 277 × 10^9 capillary segments in the human lungs have a mean diameter[39] of 5 μm; neutrophils larger than this in diameter must therefore deform to pass through this network. The same might be true of erythrocytes, which are similar in size to neutrophils, but the latter are much stiffer as a result of a more complex cytoplasm[36]. Far from being a static pool of cells, neutrophils delayed in capillary transit are in constant flux with the circulating fraction of the intravascular pool, and an inverse relationship exists between the size of the intrapulmonary pool and pulmonary arterial blood flow[40,41]. This relationship may well have pathological consequences during conditions of low flow such as haemorrhagic or septic shock. Subsequent activation of accumulated neutrophils by the action of local proinflammatory mediators may result in the development of ARDS-like capillary injury. In addition to the impedance of narrow pulmonary capillaries, changes in the cytoviscosity of the neutrophil will alter its ability to negotiate the pulmonary vascular bed. Worthen *et al.*[42] demonstrated that altering cell stiffness by neutrophil activation or pharmacological disruption of the cytoskeleton altered the cell's ability to pass through 5-μm filters. They also postulated that increase in cell stiffness, in response to activation by inflammatory mediators, is the initial mechanism by which neutrophils are sequestered in the lung after sepsis. Although recent evidence indicates this early sequestration may also be a specific receptor-mediated phenomenon, it seems likely that the physical restraints of the pulmonary capillary bed and adhesion receptor mechanisms both play a role in early neutrophil kinetic responses to sepsis.

Neutrophil chemotaxis

The distribution of neutrophils within the intravascular pool is also affected by their response to local inflammation. Numerous chemical mediators, known as chemoattractants and produced in response to local inflammation, cause the cell to move in specific directions. Thus, neutrophils can be recruited to areas of local inflammation by chemotaxis along chemical concentration gradients.

The best known[11,43] of these numerous chemoattractants are C5a (one of the cleaved protein fragments produced by activation of both the alternate and classical pathways of the complement cascade), formylmethionyl peptides of bacterial origin, platelet-activating factor and leukotriene B_4. Interleukin (IL) 8, a recently characterized proinflammatory cytokine, is the most specific and potent for neutrophils[44–46]. It is a 6·5-kDa protein of the supergene family and is produced by tissue macrophages in response to endotoxin. IL-8 is subsequently produced by fibroblasts and endothelial cells in response to other cytokines, such as tumour necrosis factor alpha (TNF-α) and IL-1, also secreted in response to endotoxin[44]. This 'networking' permits the establishment of a chemoattractant gradient across vascular endothelium, notably the alveolar capillary membrane in the lung, along which neutrophils will migrate[44,45]. The gradient is further enhanced by the flow of blood across the luminal surface of the endothelium which continually washes out IL-8, reducing its local concentration relative to the abluminal surface.

Neutrophil adhesion and migration

In response to the invasion of pathogens, neutrophils must change from loosely associated cells of the pool within the pulmonary circulation to activated cells within lung tissue, primed for phagocytosis and cell killing. This change is characterized by neutrophil adherence to, followed by migration across, the endothelial cell layer[37]. Adherence and migration rely on activation of both neutrophils and endothelial cells. This activation results in expression of a sequence of surface glycoprotein adhesion receptors whose role is to sequester neutrophils at a site of inflammation. These glycoproteins on the neutrophil surface are known as integrins[47–49]. Integrins consist of a common β_2 or cluster differentiation (CD)18 chain covalently linked to one of three different α chains (CD11a, CD11b or CD11c) and existing on the cell surface as three distinct heterodimers. CD11a–CD18 is expressed on all leucocytes whereas CD11b–CD18 and CD11c–CD18 are restricted to cells of myeloid origin[48]. Neutrophil integrins react with complementary surface proteins on stimulated endothelial cells designated endothelial cell leucocyte adhesion molecule (ELAM), intercellular adhesion molecule (ICAM) and granule membrane protein 140 (GMP-140)[50,51]. The exact nature and sequence of this interaction are unknown, although the process is currently considered to be a two-stage one[52–55] (*Figure 1*). Following exposure to proinflammatory peptides (e.g. cytokines and complement), inflamed endothelium increases its surface expression of ELAM, a protein synthesis-dependent process. The neutrophil ligand for ELAM is a member of the selectin family of adhesion receptors[56], a group of molecules with a

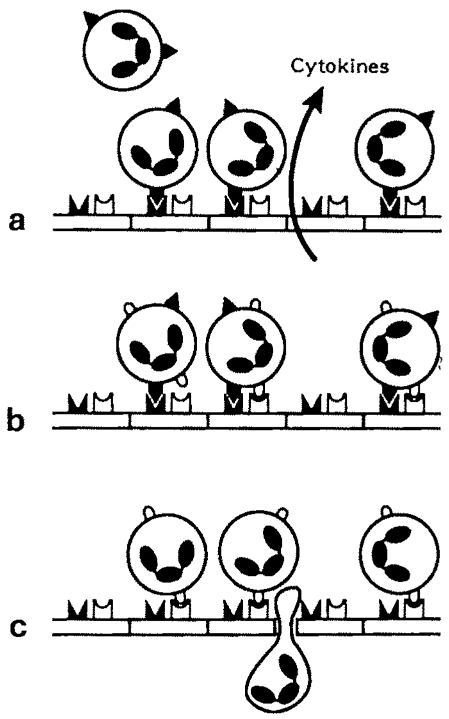


Figure 1 *Two-step migration of neutrophils across the endothelial cell layer.* **a** *Unstimulated neutrophils expressing lectin adhesion molecule (LECAM) (▼) are targeted and removed from the circulation by attachment to inflamed endothelium expressing endothelial cell leucocyte adhesion molecule (ELAM) (M).* **b** *Local chemical mediators activate the neutrophils with upregulation of cluster differentiation (CD)-11b–CD18 integrins (▯). Attachment to intercellular adhesion molecule receptors on the endothelium (⊓) provides strong adhesive forces.* **c** *Concomitant downregulation of LECAM on the neutrophil permits unopposed CD18-dependent transendothelial migration*

common *N*-terminal lectin domain that are responsible for targeting and localizing phagocytes to the site of inflammation. Designated lectin adhesion molecule (LECAM), this receptor is expressed on unstimulated neutrophils. The LECAM–ELAM binding arrests the neutrophils at the site of inflamed endothelium, removing them from the marginating pool. As a result of this process the cells are bathed in a host of locally produced inflammatory mediators and are subsequently themselves activated. This results in an upregulated expression of the CD11b–CD18 receptor, increasing both its surface number and probably receptor configuration[48]. The upregulated CD11b receptors bind to endothelial ICAM, the expression of which is also increased on the inflamed endothelium. This ligand–receptor complex provides the strong adhesive forces necessary for migration of the neutrophil across vascular endothelium[57]. Coincident with rapid upregulation of CD11b receptors is an equally rapid shedding of LECAM receptors[54], resulting in release of the initial arresting receptor complexes. Firmly established CD18–ICAM interaction then allows unopposed neutrophil migration.

It should be noted from this that both endothelial receptors ICAM and ELAM require protein synthesis for maximal expression[58,59] and are therefore likely to mediate their action late in the inflammatory process. Recent evidence suggests that the selectin GMP-140 is the key endothelial receptor mediating early neutrophil sequestration in response to inflammation. GMP-140 is stored preformed in Wiebel–Palade bodies of endothelial cells[60]. It can be mobilized to cell surfaces within minutes of endothelial activation[51] and binds to unstimulated neutrophils via the LECAM receptor[61]. Lawrence and Springer[62] demonstrated that GMP-140–LECAM interaction is probably the molecular basis of leucocyte rolling on inflamed endothelium, observed by Cohnheim[33] more than 100 years ago. They also demonstrated that this rolling–adhesion phenomenon is required for subsequent integrin–ICAM binding and migration. It is apparent, therefore, that the process of adhesion and migration is complex and requires coordinate expression of a number of surface receptors.

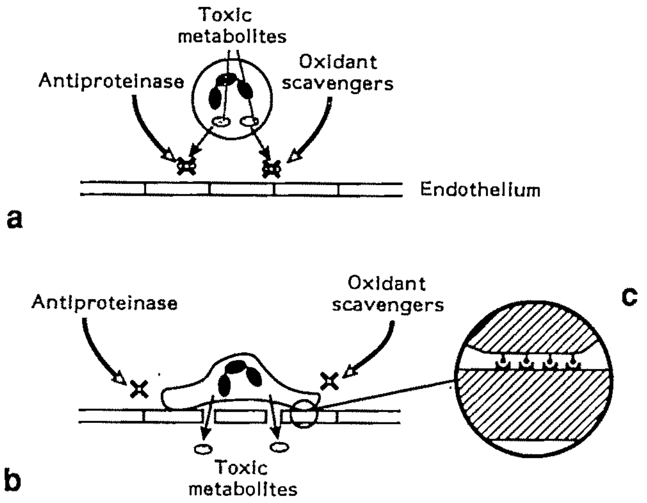


Figure 2 *Microenvironment theory of neutrophil-mediated tissue injury.* **a** *Circulating scavengers inactivate toxic neutrophil metabolites;* **b** *protected microenvironment allows endothelial injury by toxic neutrophil metabolites; and* **c** *cluster differentiation (CD)11–CD18 integrins engaged in endothelial cell leucocyte adhesion molecule or intercellular adhesion molecule receptors*

The precise stage during this sequence at which neutrophils mediate their pathological injury is unclear, although the microenvironment theory is currently popular[63] (*Figure 2*). This theory suggests that adherence of activated neutrophils to endothelium creates a microenvironment into which the cells secrete toxic products such as reactive oxidant metabolites and proteases. This microenvironment between neutrophil and endothelium is protected from the action of circulating oxidant scavengers and antiproteinases, and permits unchecked endothelial injury to develop. It is likely, however, that indiscriminate outpouring of oxidants and proteinases from neutrophils that have migrated to the interstitium in response to excessive cytokine production might also mediate significant tissue damage. Therefore, the microenvironment theory may not offer the only means of endothelial damage.

In summary, the localization of neutrophils at sites of inflammation and their subsequent activation with resultant local tissue injury is a multifaceted response. Chemotaxis, pulmonary capillary accumulation resulting from low pulmonary blood flow in shock, and specific adhesion-mediated sequestration all play a role in isolating neutrophils in the lung where they are capable of mediating the tissue injury typical of ARDS.

Cytokines

Proinflammatory mediators[5,6] that give rise to neutrophil or endothelial cell activation and enhanced adhesion receptor expression stand at the centre of the septic response. It is this complex network of cytokines, complement degradation products, eicosanoids, platelet activators and numerous other chemicals that coordinates the normal inflammatory response. It is probable that loss of control of this system allows the widespread destruction characteristic of ARDS and multisystem organ failure. A detailed description of this network is beyond the scope of this review; however, increased understanding[64–66] of the cell-derived proinflammatory peptides known as cytokines has greatly enhanced understanding of ARDS and these are mentioned here. Of the numerous cytokines characterized to date, four appear to be of primary importance in the response to sepsis: IL-8 (previously discussed), TNF-α, IL-1 and IL-6.

Tumour necrosis factor alpha

TNF-α, a proinflammatory cytokine made predominantly by cells of macrophage or monocyte lineage in response to bacterial endotoxin[67], is now recognized as a primary mediator of the host response to sepsis[68–70]. Pretreating mice[71], rabbits[72], baboons[73,74] and pigs[75] with a monoclonal antibody to TNF-α reduced mortality rates and modified the course of sepsis following administration of endotoxin or lethal numbers of Gram-negative bacteria. TNF-α activates neutrophils and upregulates adhesion receptors, which promotes neutrophil adhesion and subsequent tissue sequestration[76]. TNF-α causes neutrophil degranulation and production of toxic oxygen species while promoting differentiation of myelogenous cells to monocytes and macrophages. Endothelial cells exposed to TNF-α *in vitro* become elongated and spindle shaped, leading to the appearance of gaps between them, a defect typically observed in the lungs of patients with ARDS. TNF-α liberates arachidonic acid from membranes, promoting the formation of cyclo-oxygenase and lipoxygenase metabolites. Originally named cachectin, TNF-α plays a major metabolic role and is thought to be partly responsible for the cachexia of malignant disease[68].

Interleukin 1

IL-1 is another cytokine produced predominantly by macrophages, although it can be synthesized by a wide range of cells (with the notable exception of erythrocytes)[77]. Its biological actions overlap those of TNF-α but appear to be less dramatic[78]. It also activates neutrophils, promotes myeloid differentiation, stimulates osteoclasts and fibroblasts, and may have a role in the resolution of inflammation. Systemic injection into both animal and human subjects induces fever, hypotension, neutropenia and increased hepatic acute-phase protein synthesis[79]. Interestingly, IL-1 and TNF-α act synergistically[80] to produce hypotension and haemorrhagic lung injury at significantly lower doses than when given separately[80]. Inhibition of the activity of IL-1 by specific monoclonal antibodies that block the IL-1 receptor or the IL-1 molecule itself has also been shown to attenuate the course of sepsis[78,81].

Interleukin 6

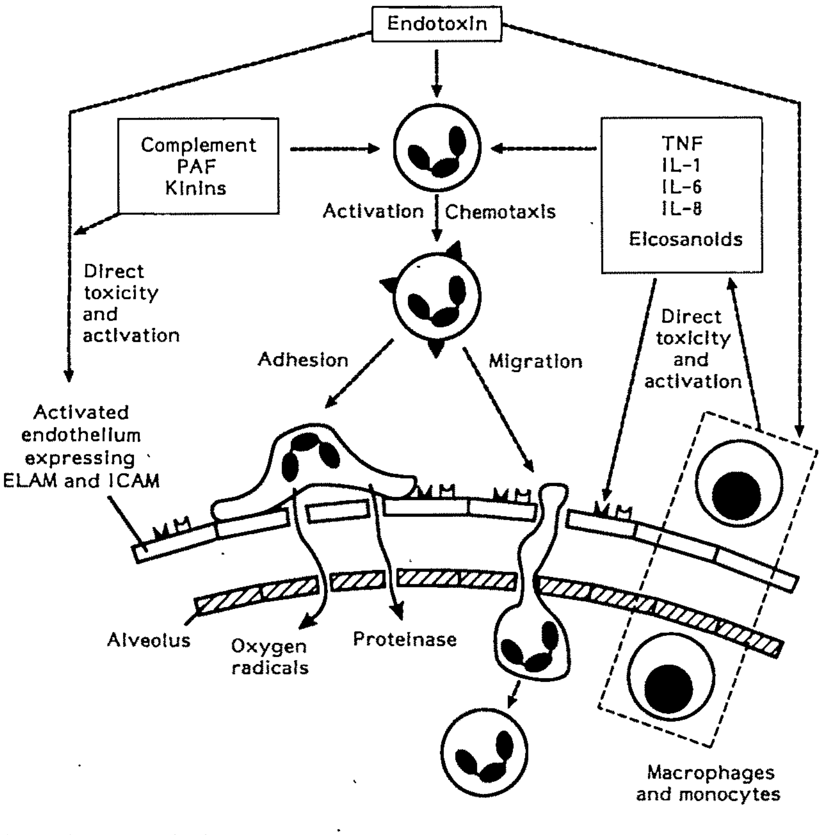
IL-6 is a pleiotropic cytokine, capable of inducing fever and modulating protein production in the liver in favour of acute-phase reactant synthesis[82–84]. It is also an important regulator of B and T cell function and stimulates differentiation of stem cells in the bone marrow. It is produced by monocytes, macrophages, endothelial cells and fibroblasts[85,86]. Production of IL-6 is induced by other cytokines[87] such as TNF-α and IL-1. Raised plasma levels of IL-6 are found in many inflammatory conditions including bacterial meningitis[88], septic shock[89], malaria[90], rheumatoid arthritis[91] and mesangial proliferative glomerulonephritis[92].

The temporal pattern of cytokine production is consistent[93,94]. IL-1 appears early in sepsis, within 1 h, followed by TNF-α at about 1–2 h and IL-6 at 3–4 h. Whereas IL-1 and TNF-α concentrations peak transiently, the IL-6 surge is sustained for a considerably longer period[94]; the importance of this in the genesis of tissue injury is uncertain, although it seems that the sequential cytokine surge is critical to the evolution of the septic response. Blocking the biological activity of an isolated cytokine by monoclonal antibody infusion not only reduces the levels of other cytokines but also attenuates end-organ damage[95,96].

Neutrophil: friend or foe?

Thus the neutrophil is a primary defence cell that is rapidly sequestered at the site of inflammation in response to stimulation by the cytokine network. In addition, it is armed with a broad range of antimicrobial mechanisms that are equally capable of mediating local host tissue injury (*Figure 3*). Evidence for its role in the genesis of ARDS is reviewed below.

In 1968, Kaplow and Goffinet[97] first noted a relationship between neutropenia developing during haemodialysis and



Endotoxin
Complement
PAF
Kinins
TNF
IL-1
IL-6
IL-8
Eicosanoids
Activation
Chemotaxis
Direct toxicity and activation
Adhesion
Migration
Direct toxicity and activation
Activated endothelium expressing ELAM and ICAM
Alveolus
Oxygen radicals
Proteinase
Macrophages and monocytes

Figure 3 *Networking of chemical mediators leads to neutrophil and endothelial cell activation with resultant alveolar capillary membrane injury. PAF, platelet-activating factor; TNF, tumour necrosis factor; IL, interleukin; ELAM, endothelial cell leucocyte adhesion molecule; ICAM, intercellular adhesion molecule*

pulmonary dysfunction. It was later hypothesized by Craddock *et al.* that systemic complement activation stimulated neutrophils and led to their sequestration in the lung microvasculature[98]. This complement theory has been superseded by evidence suggesting that endotoxin and cytokine networks act as primary chemical initiators of sepsis. However, the concept that neutrophils mediate lung damage remains a central theme of research into lung injury.

Histological evidence for the importance of the neutrophil can be obtained from autopsy study of lungs of patients who have died from ARDS. Invariably, tissue examination shows large numbers of neutrophils sequestered in the lung microvasculature[99–101]. Further evidence is provided by studies that show recovery of large numbers of neutrophils from bronchoalveolar lavage of patients suffering from ARDS[102,103]. High levels of proteinase activity are found in the same lavage fluids, suggesting that neutrophils rapidly migrated from the vascular space and were actively degranulating[104–106]. Weiland *et al.*[103] correlated the presence of neutrophils in the lavage fluid of patients with ARDS with clinically deteriorating arterial oxygen saturation. Animal experimentation has provided the bulk of the evidence supporting a role for the neutrophil in mediating lung damage. Correlations exist between the appearance of neutrophils in lavage fluid and the development of an acute peripheral neutropenia reported in numerous animal models of sepsis-induced acute lung injury[107–110]. In addition, depletion of neutrophils before injury attenuates the resulting lung damage[111–115]. Radiolabelling of neutrophils in both humans and animal models shows the cells to be quickly sequestered in the lung after the onset of sepsis[116]. More recently, functional manipulation of the neutrophil has provided striking evidence of its importance in ARDS. Inhibition of the neutrophil oxidant burst using cyclo-oxygenase inhibitors such as ibuprofen leads to attenuation of lung injury in animal models[117,118]. This occurs whether ibuprofen is used before or after injury. Monoclonal antibodies directed against the CD11b and CD18 components of the adhesion receptor complex significantly attenuate lung injury and prevent the neutropenia associated with tissue sequestration during sepsis[119,120]. These observations support the microenvironment theory of lung injury as well as incriminating the neutrophil. Preventing adherence interferes with formation of the microenvironment, while inhibiting the oxidant burst robs the neutrophil of one of its primary means of cytotoxicity. Early morphological evidence merely suggested an association between neutrophils and lung damage; this attenuation of lung injury by preventing neutrophil adhesion, activation or oxidant radical generation is indicative of a causal relationship.

Studies are by no means one-sided in favour of the neutrophil. Although not as extensive, evidence against the neutrophil being the essential cellular mediator is no less convincing. The most influential data come from isolated reports that patients who are severely neutropenic secondary to chemotherapy can still develop ARDS[121,122]. These findings suggest that other cellular or chemical mediators are capable of causing lung injury. It is interesting to note, however, that Rinaldo and Borovetz reported a further deterioration in lung mechanics with resolution of neutropenia[123]. Also, the evidence regarding recovery of neutrophils from bronchoalveolar lavage may be misleading since large numbers of such cells are seen in patients at high risk of ARDS before the syndrome becomes established, and equal numbers are seen in patients with other unrelated lung pathologies[5]. Furthermore, other authors have reported that preinsult neutrophil depletion provides no protection from lung injury[124,125]. These studies suggest that the presence of neutrophils in patients with ARDS may be only a marker not a causal agent of lung injury.

Conclusion

In summary, the evidence is contradictory and a definitive statement on the role of the neutrophil in lung injury remains elusive. Numerous authors have argued both for and against a major role with equal conviction[126–129]. The most striking evidence remains the use of monoclonal antibodies to block neutrophil adhesion receptors and the inhibition of the neutrophil oxidant burst. The reduction in tissue sequestration and attenuation of lung injury suggest a major role for the neutrophil in ARDS. However, proponents of non-neutrophil mediated injury cite ARDS in neutropenic patients as the most convincing evidence that other mechanisms are involved. Despite the current level of understanding of the pathophysiology of ARDS, the answer to the neutrophil issue remains equivocal. Undoubtedly neutrophils have a destructive potential and under certain circumstances do mediate lung injury. It seems equally clear that it is possible to generate an ARDS-like injury in the absence of neutrophils, but that the inclusion of such cells aggravates the injury. In addition, the beneficial effects of modifying neutrophil adhesion and function on the development of lung injury suggest that the cell is a 'villain' in this particular plot. Therapeutic strategies aimed at preventing these biological actions may, therefore, prove to be of benefit in a clinical setting in those patients thought to be at risk of developing ARDS.

Therapeutic implications

The realization that alveolar capillary damage is the result of a host inflammatory response has heralded a new approach to the treatment of ARDS. Early clinical trials examining the effects of monoclonal antibodies designed to block the activity of endotoxin, thus preventing the initiation or prolongation of the inflammatory response, have been completed. Results show a lower mortality rate in patients with Gram-negative septicaemia and established septic shock[130,131]. Clinical trials are currently under way to examine the efficacy of monoclonal antibodies to both TNF-α and the IL-1 receptor; early reports appear encouraging[132]. In addition, as a result of beneficial effects of neutrophil and endothelial cell adhesion receptor blockade on the development of ARDS in animal studies, it is probable that clinical trials will soon begin to examine these effects in humans.

Early results of biological response modification suggest that this strategy may provide significant clinical benefit in the future; however, a fundamental concern remains. The cellular and chemical response to sepsis is an integral part of the host immune response; inhibiting or altering this response may attenuate the resultant injury but may also expose the host to overwhelming secondary infection. This risk is illustrated by patients in whom neutrophils are deficient in the common CD18 subunit of the surface adhesion receptor, a condition known as leucocyte adhesion deficiency[133]. Such patients suffer recurrent bacterial infection and have an increased mortality rate. Animal studies also demonstrate that use of a monoclonal antibody to the CD18 receptor increases the formation of metastatic abscesses on exposure to high-dose bacterial innoculation[134]. As a consequence of this potential side-effect there has been increasing interest in attempts to modify the end-organ response to neutrophil-mediated tissue injury without affecting neutrophil or immune system function. Drugs that stabilize the endothelial monolayer by modifying the cellular cytoskeleton have been shown to attenuate permeability injury in lung and skeletal muscle following ischaemia–reperfusion[135,136]. The effect of these drugs in sepsis is currently under investigation. It may also be possible to increase the endothelial cell's ability to withstand oxidant injury by upregulating intracellular glutathione metabolism, although this possibility is as yet experimental.

Questions remain as to the future directions of ARDS research, and why only some patients at high risk of ARDS eventually develop the full-blown injury. It is unclear whether ARDS is simply a dose–response effect in which massive systemic release of cytokines and other chemical mediators, in response to a primary insult such as endotoxin, leads to large-scale activation of neutrophils and direct toxic damage that inevitably results in alveolar capillary injury. Alternatively, there may be a more complex trigger mechanism that specifically changes the immune response to one of host destruction. The next decade may well provide answers to such questions and afford the clinician more effective therapeutic agents to combat ARDS and its sequelae.

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References

1. Byrne K, Carey PD, Sugerman HJ. Adult respiratory distress syndrome. *Acute Care* 1987; **13**: 206–34.
2. Fowler AA, Hamman RF, Zerbe G, Benson KN, Hyers TM. Adult respiratory distress syndrome. *Am Rev Respir Dis* 1985; **132**: 472–4.
3. Ashbaugh DG, Bigelow DB, Petty TL *et al.* Acute respiratory distress in adults. *Lancet* 1967; **ii**: 319–23.
4. Fowler AA, Hamman RF, Good JT *et al.* Adult respiratory distress syndrome: risk with common predispositions. *Ann Intern Med* 1983; **98**: 593–7.
5. Bersten A, Sibbald WJ. Acute lung injury in septic shock. *Crit Care Clin* 1989; **5**: 49–79.
6. Rinaldo JE, Christman JW. Mechanics and mediators of adult respiratory distress syndrome. *Clin Chest Med* 1990; **2**: 621–32.
7. Weiss SJ. Tissue destruction by neutrophils. *N Engl J Med* 1989; **320**: 365–76.
8. Berger N. Oxidant induced cytotoxicity: a challenge for metabolic modulation. *Am J Respir Cell Mol Biol* 1991; **4**: 1–3.
9. McPhail LC, Dechatelet LR, Shirley PS. Further characterization of NADPH oxidase activity of human polymorphonuclear leukocytes. *J Clin Invest* 1976; **58**: 775–80.
10. Henson PM, Johnson RB. Tissue injury in inflammation: oxidants, proteinases and cationic proteins. *J Clin Invest* 1987; **79**: 669–74.
11. Lehrer H, Ganz T, Selsted ME, Babior MB, Curnutte JT. Neutrophils in host defence. *Ann Intern Med* 1988; **109**: 127–42.
12. Fridovich I. Biological effects of superoxide radical. *Arch Biochem Biophys* 1986; **247**: 1–11.
13. Hinshaw DB, Burger JH, Armstrong BC, Hyslop PA. Mechanisms of endothelial shape change in oxidant injury. *J Surg Res* 1989; **46**: 339–49.
14. Weiss SJ, Young J, LoBuglio AF, Slivka A, Nimeh NF. Role of hydrogen peroxide in neutrophil mediated destruction of cultured endothelial cells. *J Clin Invest* 1981; **68**: 714–20.
15. Weiss SJ, Klein R, Slivka A, Wei H. Chlorination of taurine: evidence for hypochlorous acid generation. *J Clin Invest* 1982; **70**: 598–607.
16. Carey PD, Byrne K, Jenkins JK *et al.* Ibuprofen attenuates hypochlorous acid production from neutrophils in porcine acute lung injury. *J Surg Res* 1990; **49**: 262–70.
17. Klebanoff SJ, Clark RA. *The Neutrophil: Function and Clinical Disorders.* Amsterdam: Elsevier/North-Holland Biomedical Press, 1978: 409–88.
18. Baggiolini M, Dewald B. The neutrophil. *Int Arch Allergy Appl Immunol* 1985; **76**: 13–20.
19. Bretz U, Baggiolini M. Biochemical and morphological characterization of azrophil and specific granules of human neutrophilic polymorphonuclear leukocytes. *J Cell Biol* 1974; **63**: 251–69.
20. Janoff A. Elastases in tissue injury. *Annu Rev Med* 1985; **36**: 207–16.
21. Anderson BO, Brown JM, Harken AH. Mechanisms of neutrophil mediated tissue injury. *J Surg Res* 1991; **51**: 170–9.
22. Carrel RW. α_1-Antitrypsin: molecular pathology, leukocytes and tissue damage. *J Clin Invest* 1986; **78**: 1427–34.
23. Umeki S, Niki Y, Soejima R. Elastase/antielastase systems in pulmonary disease. *Am J Med Sci* 1988; **296**: 103–6.
24. Brigham KL. Role of oxygen free radicals in lung injury. *Chest* 1986; **89**: 859–63.
25. Takahashi H, Nukiwa T, Basset P, Crystal RG. Myelomonocytic cell line expression of the neutrophil elastase gene. *J Biol Chem* 1988; **263**: 2543–8.
26. DuBois RM, Bernoudin JF, Paakko P. Human neutrophils express α_1-antitrypsin gene and produce α_1-antitrypsin. *Blood* 1991; **77**: 2724–3026.
27. Ossanna PJ, Test SJ, Matheson NR, Regiani S, Weiss SJ. Oxidative regulation of neutrophil elastase/α_1-proteinase inhibitor interactions. *J Clin Invest* 1986; **77**: 1939–51.
28. Matheson NR, Wong PS, Travis J. Interaction of human α_1-proteinase inhibitor with neutrophil peroxidase. *Biochemistry* 1981; **20**: 331–6.
29. Metchnikoff E. Sur la lutte des cellules de l'organisme contre l'invasion des microbes. *Annales d'Institute Pasteur* 1887; **1**: 321–36.
30. Andrews FW. The behaviour of leukocytes in infection and immunity. *Lancet* 1910; **ii**: 8–16.
31. MacNee W. Pulmonary neutrophil kinetics. *Clin Phys Physiol Meas* 1990; **11**: 133–9.
32. Boggs DR. The kinetics of neutrophilic leukocytes in health and disease. *Semin Hematol* 1967; **4**: 359–86.
33. Cohnheim J. Uber Entzundung Eiterung. *Virchows Arch A Pathol Anat Histopathol* 1867; **40**: 1.
34. Vejlens G. The distribution of leukocytes in the vascular system. *Acta Pathol Jpn* 1938; **33**: 11–33.
35. Schmid-Schönbein GW, Usami S, Skalak R, Chien S. The interaction of leukocytes and erythrocytes in capillary and post capillary vessels. *Microvasc Res* 1980; **19**: 45–70.
36. MacNee W, Selby C. Neutrophil kinetics in the lungs. *Clin Sci* 1990; **79**: 97–107.
37. Lien DC, Wagner WW, Capen RL *et al.* Physiological neutrophil sequestration in the lung: visual evidence for localization in capillaries. *J Appl Physiol* 1987; **62**: 1236–43.
38. Hogg JC. Neutrophil kinetics and lung injury. *Physiol Rev* 1987; **67**: 1249–94.
39. Weibel ER. *Morphometry of Human Lung.* New York: Academic, 1963.
40. Martin BA, Wright JL, Thommasen H, Hogg JC. Effect of pulmonary blood flow on the exchange between the circulating and marginating pool of polymorphonuclear leukocytes in dog lungs. *J Clin Invest* 1982; **69**: 1277–85.
41. Anderson BO, Brown JM, Shanley PF, Bensard DD, Harken AH. Marginating neutrophils are reversibly adherent to normal lung endothelium. *Surgery* 1991; **109**: 51–61.
42. Worthen GS, Schwab B, Elson EL, Downey GP. Mechanics of stimulated neutrophils: cell stiffening induces retention in capillaries. *Science* 1989; **245**: 183–6.
43. Demling RM. The role of mediators in adult respiratory distress syndrome. *J Crit Care* 1988; **3**: 56–72.
44. Kunkel SL, Standiford T, Kasahara K, Streiter RM. Interleukin-8: the major neutrophil chemotactic factor in the lung. *Exp Lung Res* 1991; **17**: 17–23.
45. Van Zee KJ, DeForge LE, Fischer E *et al.* IL-8 in septic shock, endotoxaemia and after IL-1 administration. *J Immunol* 1991; **146**: 3478–82.
46. Baggiolini M, Walz A, Kunkel SL. Neutrophil-activating peptide-1/IL-8, a novel cytokine that activates neutrophils. *J Clin Invest* 1989; **84**: 1045–9.
47. Springer T. Adhesion receptors of the immune system. *Nature* 1990; **346**: 425–33.
48. Carlos T, Harlan JM. Membrane protein involved in phagocyte adherence to endothelium. *Immunol Rev* 1990; **114**: 5–28.
49. Larson RS, Springer TA. Structure and function of leukocyte integrins. *Immunol Rev* 1990; **114**: 181–217.
50. Albelda SM. Endothelial and epithelial cell adhesion molecules. *Am J Respir Cell Mol Biol* 1991; **4**: 195–203.
51. McEver RP. GMP-140: a receptor for neutrophils and monocytes on activated platelets and endothelium. *J Cell Biochem* 1991; **45**: 156–61.
52. Kishimoto TK, Warnock RA, Jutila MA *et al.* Antibodies against human neutrophil LECAM-1 and endothelial cell ELAM-1 inhibit a common CD18 independent adhesion pathway *in vitro*. *Blood* 1991; **78**: 805–11.
53. Smith CW, Kishimoto TK, Abbass O *et al.* Chemotactic factors regulate lectin adhesion molecule-1 (LECAM-1) dependent neutrophil adhesion to cytokine-stimulated endothelial cells *in vitro*. *J Clin Invest* 1991; **87**: 609–18.
54. von Adrian UH, Chambers DJ, McEvoy LM, Bargatze RF, Arfors KE, Butcher EC. Two step model of leukocyte–endothelial cell interaction in inflammation: distinct roles for LECAM-1 and leukocyte β_2 integrins *in vivo*. *Proc Natl Acad Sci U S A* 1991; **88**: 7538–42.

55. Kishimoto TK. A dynamic model for neutrophil localization to inflammatory sites. *Journal of National Institute of Health Research* 1991; **3**: 75–7.
56. Springer TA. Sticky sugars for selectins. *Nature* 1991; **349**: 196–7.
57. Smith CW, Marlin SD, Rothlein R, Toman C, Anderson DC. Co-operative interaction of LFA-1 and MAC-1 with ICAM in facilitating adherence and transendothelial migration. *J Clin Invest* 1989; **83**: 2008–17.
58. Diamond MS, Saunton DE, de Fougerolles AR *et al.* ICAM-1 (CD54): a counter receptor for Mac-1 (CD11b/CD18). *J Cell Biol* 1990; **111**: 3129–39.
59. Bevilacqua MP, Stengelin F, Gimbrone MA, Seed B. ELAM-1: an inducible receptor for neutrophils related to complement regulatory proteins and lectins. *Science* 1989; **243**: 1160–5.
60. Bonfanti R, Furie BC, Furie B, Wagner DD. PADGEM (GMP-140) is a component of Weibel–Palade bodies of human endothelial cells. *Blood* 1989; **73**: 1109–12.
61. Picker LJ, Warnock RA, Burns AR, Doerschuk CM, Berg EL, Butcher EC. The neutrophil selectin LECAM-1 presents carbohydrate ligands to the vascular selectins ELAM-1 and GMP-140. *Cell* 1991; **66**: 921–33.
62. Lawrence MB, Springer TA. Leukocytes roll on a selectin at physiological flow rates: distinction from and prerequisite for adhesion through integrins. *Cell* 1991; **65**: 859–73.
63. Harlan JM. Neutrophil mediated vascular injury. *Acta Medica Scandinavica Supplement* 1987; **715**: 123–9.
64. Jacobs RF, Tabor DR. Immune cellular interactions during sepsis and septic injury. *Crit Care Clin* 1989; **5**: 9–23.
65. Brown JM, Grosso MA, Harken AH. Cytokines, sepsis and the surgeon. *Surg Gynecol Obstet* 1989; **169**: 568–75.
66. Mantovani A, Dejana E. Cytokines as communication signals between leukocytes and endothelial cells. *Immunol Today* 1989; **10**: 370–4.
67. Kelley J. Cytokines of the lung. *Am Rev Respir Dis* 1990; **141**: 765–88.
68. Rock CS, Lowry SF. Tumour necrosis factor. *J Surg Res* 1991; **51**: 434–45.
69. Michie HR, Guillou PJ, Wilmore DW. Tumour necrosis factor and bacterial sepsis. *Br J Surg* 1989; **76**: 670–1.
70. Michie HR, Wilmore DW. Sepsis and tumor necrosis factor – bedfellows that cannot be ignored. *Ann Surg* 1990; **212**: 653–4.
71. Silva AT, Bayston KF, Cohen J. Prophylactic and therapeutic effects of a monoclonal antibody to tumor necrosis factor-α in experimental Gram-negative shock. *J Infect Dis* 1990; **162**: 421–7.
72. Mathison JC, Wolfson E, Ulevitch RJ. Participation of tumor necrosis factor in the mediation of Gram-negative bacterial lipopolysaccharide-induced injury in rabbits. *J Clin Invest* 1988; **81**: 1925–37.
73. Tracey KJ, Fong Y, Hesse DG *et al.* Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature* 1987; **330**: 662–4.
74. Hinshaw LB, Tekamp-Olson P, Chang AC *et al.* Survival of primates in LD$_{100}$ septic shock following therapy with antibody to tumor necrosis factor (TNFα). *Circ Shock* 1990; **30**: 279–92.
75. Walsh CJ, Sugerman HJ, Mullen PG *et al.* Monoclonal antibody to tumour necrosis factor-α attenuates cardiopulmonary dysfunction in porcine Gram-negative sepsis. *Arch Surg* 1992; **127**: 138–44.
76. Salyer JL, Bohnsack JF, Knape WA, Shigeoka AO, Ashwood ER, Hill HR. Mechanisms of tumor necrosis factor-α alteration of PMN adhesion and migration. *Am J Pathol* 1990; **136**: 831–41.
77. Mizel SB. The interleukins. *FASEB J* 1989; **3**: 2379–88.
78. Dinarello CA. Interleukin-1 and interleukin-1 antagonism. *Blood* 1991; **77**: 1627–52.
79. Okusawa S, Gelfand JA, Ikejima T, Connolly RJ, Dinarello CA. Interleukin-1 induces a shock-like state in rabbits. *J Clin Invest* 1988; **81**: 1162–72.
80. Ferrante A, Nanadoskar M, Walz A, Goh DHB, Kowanko IC. Effects of tumour necrosis factor alpha and interleukin 1 on human neutrophil migration, respiratory burst and degranulation. *Int Arch Allergy Appl Immunol* 1988; **86**: 82–91.
81. Wakabyashi G, Gelfand JA, Burke JF, Thompson RC, Dinarello CA. A specific receptor antagonist for interleukin-1 prevents *E. coli* induced shock in rabbits. *FASEB J* 1991; **5**: 338–43.
82. Geiger T, Andus T, Klapproth J, Hirano T, Kishimoto T, Heinrich P. Induction of rat acute protein synthesis by interleukin-6 *in vivo*. *Eur J Immunol* 1988; **18**: 717–21.
83. Marinkovic S, Jahreis GP, Wong GG, Baumann H. IL-6 modulates the synthesis of a specific set of acute phase plasma proteins *in vivo*. *J Immunol* 1989; **142**: 808–12.
84. Perlmutter DH, May LT, Sehgal PB. Interferon β_2/interleukin-6 modulates synthesis of α_1-antitrypsin in human mononuclear phagocytes and in human hepatoma cells. *J Clin Invest* 1989; **84**: 138–44.
85. May LT, Ghrayeb J, Santhanam U *et al.* Synthesis and secretion of multiple forms of 'β_2-interferon/B-cell differentiation factor BSF-2/hepatocyte stimulating factor' by human fibroblasts and monocytes. *J Biol Chem* 1988; **263**: 7760–4.
86. Sironi M, Breviario F, Prosperio P *et al.* IL-1 stimulates IL-6 production in endothelial cells. *J Immunol* 1989; **142**: 549–51.
87. Kasid A, Director EP, Rosenberg SA. Regulation of interleukin-6 (IL-6) production by IL-2 and TNF-α in human peripheral blood mononuclear cells. *Ann N Y Acad Sci* 1989; **557**: 564–6.
88. Waage A, Brandtzaeg P, Halstensen A, Kierulf P, Espevik T. The complex pattern of cytokines in serum from patients with meningococcal septic shock. *J Exp Med* 1989; **169**: 333–8.
89. Calandra T, Gerain J, Heumann D, Baumgartner J, Glauser MP. High circulating levels of interleukin-6 in patients with septic shock: evolution during sepsis, prognostic value and interplay with other cytokines. *Am J Med* 1991; **91**: 23–9.
90. Kern P, Hemmer CJ, Van Damme J, Gruss H, Dietrich M. Elevated tumor necrosis factor alpha and interleukin-6 serum levels as markers for complicated *Plasmodium falciparum* malaria. *Am J Med* 1989; **87**: 139–43.
91. Hirano T, Matsuda T, Turner M *et al.* Excessive production of interleukin-6/B cell stimulatory factor-2 in rheumatoid arthritis. *Eur J Immunol* 1988; **18**: 1797–801.
92. Horii Y, Muraguchi A, Iwano M *et al.* Involvement of IL-6 in mesangial proliferative glomerulonephritis. *J Immunol* 1989; **143**: 3949–55.
93. Fong Y, Moldawer LL, Marano M *et al.* Endotoxemia elicits increased circulating β_2-IFN/IL-6 in man. *J Immunol* 1989; **42**: 2321–4.
94. Hesse DG, Tracey KJ, Fong Y *et al.* Cytokine appearance in human endotoxemia and primate bacteremia. *Surg Gynecol Obstet* 1990; **166**: 147–55.
95. Starnes HF, Pearce MK, Tewari A, Yim JH, Zou J, Abrams JS. Anti IL-6 monoclonal antibodies protect against lethal *E. coli* and lethal TNF challenge in mice. *J Immunol* 1990; **145**: 4185–91.
96. Fong Y, Tracey KJ, Moldawer LL *et al.* Antibodies to cachectin/TNF reduce interleukin 1 and interleukin 6 appearance during lethal bacteraemia. *J Exp Med* 1989; **170**: 1627–33.
97. Kaplow LS, Goffinet JA. Profound neutropenia during the early phase of haemodialysis. *JAMA* 1968; **203**: 1135–7.
98. Craddock PR, Fehr J, Brigham KL, Kronenberg RS, Jacob HS. Complement and leukocyte mediated pulmonary dysfunction in haemodialysis. *N Engl J Med* 1977; **59**: 721–30.
99. Riede UN, Joachim H, Hassenstein J *et al.* The pulmonary air–blood flow barrier of human shock lungs. *Pathol Res Pract* 1978; **162**: 41–72.
100. Bachofen M, Weibel ER. Alterations of the gas exchange apparatus in adult respiratory insufficiency associated with septicaemia. *Am Rev Respir Dis* 1977; **116**: 589–615.
101. Orell SR. Lung pathology in respiratory distress following shock in adults. *APMIS* 1971; **79**: 65–76.
102. Fowler AA, Hyers TM, Fischer J *et al.* The adult respiratory distress syndrome: cell populations and soluble mediators in the air spaces of patients at high risk. *Am Rev Respir Dis* 1987; **136**: 1225–31.
103. Weiland JE, Davis WB, Holter JF *et al.* Lung neutrophils in the adult respiratory distress syndrome. *Am Rev Respir Dis* 1986; **133**: 218–25.
104. Lee CT, Fein AM, Lippman M, Holtzman H, Kimbel P, Wienbaum G. Elastolytic activity in pulmonary lavage fluid from patients with adult respiratory distress syndrome. *N Engl J Med* 1981; **304**: 192–6.
105. McGuire WW, Spragg RG, Cohen AM, Cochrane CG. Studies on the pathogenesis of the adult respiratory distress syndrome. *J Clin Invest* 1982; **69**: 543–53.
106. Fowler AA, Walchak S, Giclas PC, Heines PH, Hyers TM. Characterization of antiproteinase activity in adult respiratory distress syndrome. *Chest* 1982; **81**(Suppl): 50–1.
107. Brigham KL, Woolverton WC, Blake LH, Staub NC. Increased sheep lung vascular permeability caused by pseudomonas bacteremia. *J Clin Invest* 1974; **54**: 792–804.
108. Meyrick B, Brigham KL. Acute effects of *E. coli* endotoxin on

the pulmonary microcirculation of anesthetized sheep. *Lab Invest* 1983; **48**: 458–70.
109. Jenkins J, Carey PD, Byrne K, Sugerman HJ, Fowler AA. Sepsis induced lung injury and the effects of ibuprofen pretreatment. *Am Rev Respir Dis* 1991; **143**: 155–61.
110. Walsh CJ, Leeper-Woodford SK, Carey PD *et al.* CD18 adhesion receptors, tumor necrosis factor and neutropenia during septic lung injury. *J Surg Res* 1991; **50**: 323–9.
111. Flick MR, Percel A, Staub NC. Leukocytes are required for increased lung microvascular permeability after microembolization in sheep. *Circ Res* 1981; **48**: 344–51.
112. Johnson A, Malik AB. Effect of granulocytopenia on extravascular lung water content after microembolization. *Am Rev Respir Dis* 1980; **122**: 561–6.
113. Helfin AC, Brigham KL. Prevention by granulocyte depletion of increased vascular permeability of sheep lung following endotoxemia. *J Clin Invest* 1981; **68**: 1253–60.
114. Stephens KE, Ishizaka A, Wu Z, Larrick JW, Raffin TA. Granulocyte depletion prevents TNF mediated acute lung injury in guinea pigs. *Am Rev Respir Dis* 1988; **138**: 1300–7.
115. Hinson JM, Hutchinson AA, Ogletree ML *et al.* Effect of granulocyte depletion on altered lung mechanics after endotoxaemia in sheep. *J Appl Physiol* 1983; **55**: 92–9.
116. Hangen DH, Segall GM, Harney EW, Stevens JH, McDougal IR, Raffin TA. Kinetics of leukocyte sequestration in the lungs of acutely septic primates: a study using ^{111}In-labelled autologous leukocytes. *J Surg Res* 1990; **48**: 196–203.
117. Carey PD, Leeper-Woodford SK, Walsh CJ, Byrne K, Fowler AA, Sugerman HJ. Delayed cyclooxygenase blockade reduces the neutrophil respiratory burst and tumour necrosis factor levels in sepsis-induced acute lung injury. *J Trauma* 1991; **31**: 733–41.
118. Carey PD, Byrne K, Jenkins JK *et al.* Ibuprofen attenuates hypochlorous acid production from neutrophils in porcine acute lung injury. *J Surg Res* 1990; **49**: 262–70.
119. Ismail G, Morganroth ML, Todd RF, Boxer LA. Prevention of pulmonary injury in isolated perfused rat lung by activated human neutrophils preincubated with anti-Mo1 monoclonal antibody. *Blood* 1987; **69**: 1167–74.
120. Walsh CJ, Carey PD, Cook DJ, Bechard DE, Fowler AA, Sugerman HJ. Anti-CD18 antibody attenuates neutropenia and alveolar capillary membrane injury during Gram-negative sepsis. *Surgery* 1991; **110**: 205–12.
121. Maunder RJ, Hackman RC, Riff E, Albert RK, Springmeyer SC. Occurrence of adult respiratory distress syndrome in neutropenic patients. *Am Rev Respir Dis* 1986; **133**: 313–16.
122. Ognibene FC, Martin SE, Parker MM. Adult respiratory distress syndrome in patients with severe neutropenia. *N Engl J Med* 1986; **315**: 547–51.
123. Rinaldo JE, Borovetz H. Deterioration of oxygenation and abnormal lung microvascular injury during resolution of leukopenia in patients with diffuse lung injury. *Am Rev Respir Dis* 1985; **131**: 579–83.
124. Pingleton WW, Coalson JJ, Guenter CA. Significance of leukocytes in endotoxic shock. *Exp Mol Pathol* 1975; **22**: 183–94.
125. Schwartz BA, Niewohner DE, Hoidal JR. Neutrophil depletion does not protect rats from hyperoxic injury. *Clin Res* 1983; **31**: 746A.
126. Brigham KL, Meyrick B. Endotoxin and lung injury. *Am Rev Respir Dis* 1986; **133**: 913–27.
127. Swank DW, Moore SB. Role of the neutrophil and other mediators in adult respiratory distress syndrome. *Mayo Clin Proc* 1989; **64**: 1118–32.
128. Brigham KL, Meyrick B. Granulocyte dependent injury of pulmonary endothelium: a case of miscommunication. *Tissue Cell* 1984; **16**: 137–55.
129. Tate RM, Repine JE. Neutrophils and the adult respiratory distress syndrome. *Am Rev Respir Dis* 1983; **128**: 552–9.
130. Ziegler EJ, Fisher CJ, Sprung CL, Straube RC, Sadoff JC, Foulke GE. Treatment of Gram-negative bacteraemia and septic shock with HA-1A human monoclonal antibody against endotoxin. *N Engl J Med* 1991; **324**: 429–36.
131. Greenman RL, Schein RMH, Martin MA *et al.* A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of Gram-negative sepsis. *JAMA* 1991; **266**: 1097–102.
132. Exley AR, Cohen J, Buurman W *et al.* Monoclonal antibody to TNF-α in severe septic shock. *Lancet* 1990; **335**: 1275–7.
133. Arnaout MA. Leukocyte adhesion molecule deficiency: its structural basis, pathophysiology and implication for modulating the inflammatory response. *Immunol Rev* 1990; **114**: 145–80.
134. Sharar SR, Robert KW, Murry CE, Harlan JM, Rice CL. A CD18 monoclonal antibody increases the incidence and severity of subcutaneous abscess formation after high dose *S. aureus* injection in rabbits. *Surgery* 1991; **110**: 213–20.
135. Goldman G, Welbourn R, Alexander S *et al.* Modulation of pulmonary permeability *in vivo* with agents that affect the cytoskeleton. *Surgery* 1991; **109**: 533–8.
136. Korthius RJ, Carden DL, Kvietys PR, Shepro D, Fuseler J. Phalloidin attenuates postischaemic neutrophil infiltration and increases microvascular permeability. *J Appl Physiol* 1991; **71**: 1261–9.

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Contemporary management of the appendiceal mass

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An appendiceal mass is the end result of a walled-off appendiceal perforation and represents a pathological spectrum ranging from phlegmon to abscess. Over the past decade, improved imaging and interventional radiological techniques have allowed a more accurate definition of pathology and thus a more specific and less invasive management than was previously possible. A management policy should be possible that allows over 80 per cent of patients presenting with an appendiceal mass to be safely spared an open operation.

Acute appendicitis, the most common cause of an acute abdomen requiring surgery, is complicated by the development of a periappendicular mass in 2–6 per cent of cases[1]. The appendiceal mass is the end result of a walled-off appendiceal perforation. Pathologically it may represent a spectrum ranging from phlegmon to abscess. The former is an inflammatory tumour consisting of the inflamed appendix, its adjacent viscera and the greater omentum. The latter is a pus-containing appendiceal mass. Patients who have appendicitis and a mass tend to have a longer duration of symptoms and present to medical attention after 5–7 days; the condition is probably seen less commonly nowadays as a result of improved patient and physician education[1,2]. Fever and white blood cell count are higher than in uncomplicated appendicitis. However, clinical distinction between a periappendicular phlegmon and a liquefied appendicular abscess is notoriously difficult[3]. At operation, appendiceal masses are found to contain from none to a few hundred millilitres of pus[4]; between a classical phlegmon and a typical abscess there is a 'grey area' of intermediate clinical characteristics and natural history. Occasionally, because of abdominal wall guarding and/or obesity, the mass becomes palpable only when the patient is anaesthetized for operation[4]. All these factors have resulted in confusion in the literature, which often lacks consistency in using the terms appendiceal mass and abscess[5]: many authors incorrectly use 'abscess' to describe the whole spectrum of appendiceal masses[6–10].

Evolution of treatment

Although the operative treatment of acute appendicitis is widely accepted, management of the condition complicated by a palpable mass has evoked controversy for more than 100 years. Murphy encouraged a limited operation with drainage of pus and removal of the appendix 'if it be accessible and easily amputated'[11]. He was also the first to recommend interval appendicectomy after simple abscess drainage, during a 'quiet period'[11]. In the early years of this century, an initial non-operative approach was introduced by Ochsner[12] because of the fear that infection would be spread by early surgical intervention. Simple drainage was performed in patients suspected of having an abscess and elective interval appendicectomy practised at a later stage to prevent recurrent appendicitis[13]. A few decades later, with improved anaesthesia, better supportive care, and the introduction of antibiotic therapy, surgeons advocated immediate operation and appendicectomy for any stage of acute appendicitis.

Protagonists of immediate appendicectomy claimed that the procedure could be performed safely and that the total hospital stay was reduced by eliminating the readmission for interval appendicectomy[4,14,15]. In addition, patients were spared the risk of recurrent appendicitis and the inconvenience and morbidity of elective appendicectomy[7]. Advocates of the conservative approach stressed, on the other hand, that early appendicectomy may disseminate infection and that the procedure could be hazardous. Dissecting out the conglomerate of inflamed oedematous tissue could damage nearby bowel and result in a fistula[7,15]. Furthermore, the inflammatory appendiceal mass may be mistaken for a malignant caecal tumour; this occasionally resulted in unnecessary right hemicolectomy[14,16].

Currently the preferred approach to an appendiceal mass appears to be conservative[5,8,10,11,17]. Conventional management policy is described in a recent edition of a popular surgical textbook[2]: the patient is placed on a regimen of bed rest, maintained on fluids only, with broad-spectrum antibiotics given intravenously. The majority of masses resolve on this regimen. Should the swelling and/or signs of infection persist, the diagnosis of an abscess is established and this is drained, preferably via an extraperitoneal approach. Appendicectomy is performed only 'if the appendix readily comes to hand'. Whether resolution occurs or whether surgical drainage is required, elective appendicectomy is recommended after an interval of about 8 weeks.

Advances in diagnostic abdominal imaging and invasive radiological techniques have revolutionized the general management of abdominal abscesses. This review examines the impact of these developments on the modern treatment of the appendiceal mass. In addition, the present role of interval appendicectomy is critically scrutinized.

Modern imaging of an appendiceal mass

Reports comparing the results of various imaging techniques for the appendiceal mass are difficult to assess as both phlegmon and abscess tend to be included indiscriminately. The inability to distinguish accurately between the two hampers decision making and complicates treatment. Accumulated experience suggests that the use of non-invasive imaging by ultrasonography and computed tomography (CT) provides early accurate diagnosis and enables an appropriate initial clinical management[3,18–23].

Bagi *et al.* used abdominal ultrasonography in 40 patients with an appendiceal mass. An abscess was diagnosed as a rounded or irregularly outlined sonolucent structure containing small echogenic particles close to the caecum. If only thick-walled liquid-containing intestine or nothing abnormal was noted, the mass was regarded as a phlegmon[18,19]. Nine patients diagnosed as having an appendiceal phlegmon recovered without treatment. In the remaining 31 an abscess

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was diagnosed. Fourteen of these patients were initially managed conservatively: 12 recovered, one was subsequently operated on for suspected, but not verified, free perforation and the last underwent surgery for intestinal obstruction. The remaining 17 patients with abscesses were treated by percutaneous catheter drainage: 16 recovered uneventfully and one was operated on for suspected, but again unverified, intraperitoneal rupture[18,19]. Others have uncovered various problems with ultrasonography (the sonographic appearance may be variable with echogenic abscess and sonolucent phlegmon) and have suggested that contrast-enhanced CT is a more reliable method for differentiating phlegmon from liquefied pus[3,20–23].

On contrast-enhanced CT, periappendiceal phlegmons appear as soft tissue high-density masses, while abscesses are significantly lower in density. Contrast enhancement is essential to discriminate between areas of solid inflammatory tissue and liquid pus[3]. Visualization of an appendicolith is a finding specific for appendicitis[24].

Selection of management

Based on their appearance on CT, Jeffrey separated appendiceal masses into three categories that influenced clinical management[3]. Phlegmons and abscesses <3 cm in maximum diameter were defined as group I, larger but well localized abscesses as group II and extensive periappendicular abscesses involving multiple intraperitoneal or extraperitoneal compartments as group III. Thirty-two patients in group I were treated solely with antibiotics, giving complete resolution of inflammation in 88 per cent. Group II comprised 28 cases; CT-guided percutaneous catheter drainage was successful in 26. Two patients had small recurrent abscesses a few weeks after drainage that resolved completely with further antibiotic therapy. Ten patients were placed in group III; all underwent surgical drainage, with one death from sepsis. Interestingly, of the nine surviving patients, three had false-positive CT diagnoses of periappendicular abscess, the correct diagnoses respectively being ruptured caecal lymphoma, perforated caecal diverticulum and ruptured ovarian cyst. The high success rate of CT-guided percutaneous drainage for appendiceal mass has been confirmed by others[20–22,25].

As after surgical drainage of an appendiceal abscess, a caecal fistula may also develop following percutaneous drainage[21]. Nunez *et al.* performed tube abscessograms in 19 cases; bowel communication was revealed in five[22]. These low-output fistulas to the caecum or base of the appendix are of little clinical significance because all eventually undergo spontaneous closure[3].

Role of elective interval appendicectomy

Classically, following the successful non-operative management of an appendiceal phlegmon or after the simple drainage of an appendiceal abscess, elective interval appendicectomy was performed[11]. Such a policy, although recommended even today[2], has recently been questioned[5,6,8,13,17,18]. The apparent role of interval appendicectomy is to prevent repeated episodes of acute appendicitis and to eliminate the possibility of missing the true diagnosis of other conditions masquerading as an appendiceal mass.

The mean reported incidence of recurrent appendicitis in a collected series of 329 patients managed conservatively during the past three decades was 13·7 (range 0–20) per cent. The danger of recurrence[17] is greatest during the first year after the initial episode and minimal after 2 years.

The incidence of other pathologies labelled initially as an appendiceal mass has been reported[17] to be 0–12 per cent. The list of misdiagnosed entities is long and includes benign and malignant tubo-ovarian conditions, mesenteric tumours, carcinoid of the appendix[6], pancreatic pseudocyst[17], regional enteritis[14] and ruptured caecal diverticulum[23]. However, the main source of anxiety is a malignant caecal tumour that presents initially as an inflammatory appendiceal mass[6,7,14,23,26]. Consequently, most authors believe that patients over the age of 40–50 years should undergo routine barium enema examination or colonoscopy after resolution of the acute episode[17,22,26]. Patients with continuous symptoms, in the face of normal colonic studies, should be investigated with repeat abdominal CT or even laparotomy. Theoretically, routine elective appendicectomy may be safely omitted in more than 80 per cent of patients[17].

Conclusions

During the past decade, improved imaging and interventional radiological techniques have allowed more accurate distinction between appendiceal phlegmon and abscess, and thus more specific and less invasive management. All patients presenting with an appendiceal mass should initially be treated conservatively. In the absence of rapid improvement, or when clinical features of an abscess are present, abdominal ultrasonography or CT should be performed. When a phlegmon or small abscess is demonstrated, conservative treatment should be continued. Larger abscesses are best treated with percutaneous drainage, while complex multilocular abscesses should be managed by open operation[27], preferably via an extraperitoneal approach[28]. When rapid clinical improvement does not follow, or when the diagnosis of intra-abdominal infection from other sources is entertained, operative intervention should not be delayed[29]. Routine elective interval appendicectomy is not recommended. However, patients over the age of 40 years should be followed with appropriate radiological studies to exclude abdominal malignancy.

Nowadays an appendiceal mass, treated either conservatively or by operation, very seldom leads to death. Similarly, elective resection of the appendix is a safe operation. Therefore, other measurements of the efficacy of the therapeutic choices must be used. The morbidity rates and cost–effectiveness of the various approaches are difficult to assess from the available retrospective reports. Sadly, there is a lack of properly designed prospective randomized studies, and so the therapeutic options available today cannot be compared with confidence. However, from the data presented here, it is clear that over 80 per cent of patients presenting with an appendiceal mass might in principle be spared the inconvenience of open surgical intervention. This aim is logical and such an approach is safe. It should be adopted.

References

1. Arnbjornsson E. Management of appendiceal abscess. *Current Surgery* 1984; **41**: 4–9.
2. Ellis H. Appendix. In: Schwartz SI, Ellis H, eds. *Maingot's Abdominal Surgery*. Norwalk, Connecticut: Appleton–Century–Crofts, 1989: 967–9.
3. Jeffrey RB. Management of the periappendiceal inflammatory mass. *Semin Ultrasound CT MR* 1989; **10**: 341–7.
4. Vakili C. Operative treatment of appendix mass. *Am J Surg* 1976; **131**: 312–13.
5. Skoubo-Kristensen E, Hvid I. The appendiceal mass. *Ann Surg* 1982; **196**: 584–7.
6. Mosegaard A, Nielsen OS. Interval appendectomy. *Acta Chirurgica Scandinavica* 1979; **145**: 109–11.
7. Paull DL, Bloom PG. Appendiceal abscess. *Arch Surg* 1982; **117**: 1017–19.
8. Lewin J, Fenyö G, Engstrom L. Treatment of appendiceal abscess. *Acta Chirurgica Scandinavica* 1988; **154**: 123–5.
9. Bradely EL, Isaacs J. Appendiceal abscess revisited. *Arch Surg* 1978; **113**: 130–2.
10. Hoffmann J, Rolff M, Lomborg V, Franzmann M. Ultraconservative management of appendiceal abscess. *J R Coll Surg Edinb* 1991; **36**: 18–20.
11. Murphy JB. Two thousand operations for appendicitis. *Am J Med Sci* 1904; **128**: 187–211.
12. Ochsner AJ. The cause of diffuse peritonitis complicating appendicitis and its prevention. *JAMA* 1901; **26**: 1747–54.
13. Ranson JHC. Nonoperative treatment of the appendiceal mass:

progress of regression? *Gastroenterology* 1987; **93**: 1439–45.
14. Foran B, Berne TV, Rosoff L. Management of the appendiceal mass. *Arch Surg* 1978; **113**: 1144–5.
15. Jordan JS, Kovalcik PJ, Schwab CW. Appendicitis with a palpable mass. *Ann Surg* 1981; **193**: 227–9.
16. Riseman JA, Wichterman K. Evaluation of right hemicolectomy for unexpected cecal mass. *Arch Surg* 1989; **124**: 1043–4.
17. Hoffmann J, Lindhard A, Jensen HE. Appendix mass: conservative management without interval appendectomy. *Am J Surg* 1984; **148**: 379–82.
18. Bagi P, Dueholm S. Nonoperative management of the ultrasonically evaluated appendiceal mass. *Surgery* 1987; **101**: 602–5.
19. Bagi P, Dueholm S, Karstrup S. Percutaneous drainage of appendiceal abscess. *Dis Colon Rectum* 1987; **30**: 532–5.
20. van Sonnenberg E, Wittich GR, Casola G *et al.* Periappendiceal abscesses: percutaneous drainage. *Radiology* 1987; **163**: 23–6.
21. Johnson WC, Gerzof SG. Appendiceal abscess: operative drainage or percutaneous drainage? *Infections in Surgery* 1985; May: 367–70.
22. Nunez D, Yrizarry JM, Casillas VJ, Becerra J, Russell E. Percutaneous management of appendiceal abscesses. *Semin Ultrasound CT MR* 1989; **10**: 384–51.
23. Barakos JA, Jeffrey RB, Federle MP, Wing VW, Laing FC, Hightower DR. CT in the management of periappendicular abscess. *AJR Am J Roentgenol* 1986; **146**: 1161–4.
24. Brown JJ. Acute appendicitis: the radiologist's role. *Radiology* 1991; **180**: 13–14.
25. Flancbaum L, Nosher JL, Brolin RE. Percutaneous catheter drainage of abdominal abscesses associated with perforated viscus. *Am Surg* 1990; **56**: 52–6.
26. Bleker RJ, Wereldsma JC. Colonic malignancy mimicking an appendiceal mass. *Neth J Surg* 1989; **41**: 42–6.
27. Malangoni MA, Shumate CR, Thomas HA, Richardson JD. Factors influencing the treatment of intra-abdominal abscesses. *Am J Surg* 1990; **159**: 167–71.
28. Stone HH, Mullins RJ, Dunlop WE, Strom PR. Extraperitoneal *versus* transperitoneal drainage for the intra-abdominal abscess. *Surg Gynecol Obstet* 1984; **159**: 549–52.
29. Brolin RE, Flancbaum L, Ercoli FR *et al.* Limitations of percutaneous catheter drainage of abdominal abscesses. *Surg Gynecol Obstet* 1991; **173**: 203–10.

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Intraoperative streptokinase: a useful adjunct to balloon-catheter embolectomy

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Intraoperative thrombolysis was attempted in 31 acutely ischaemic legs after operative arteriography had demonstrated residual distal thrombus or occlusion following balloon-catheter thromboembolectomy. There were 30 patients, 16 men and 14 women, aged 43–82 (median 73) years. The indication for operation was severe ischaemia with sensorimotor loss in 25 limbs, failed percutaneous thrombolysis in three and acute graft occlusion in three. A total of 21 perfemoral, 11 perpopliteal and four graft embolectomies were initially performed. Following arteriography, 100 000 units streptokinase was infused down the isolated distal arterial tree over 30 min and arteriography repeated. Complete lysis was achieved in 11 legs (35 per cent) and partial lysis in 12 (39 per cent). Additional procedures required included six operative angioplasties and six bypass grafts. After operation pedal pulses were restored in 14 limbs (45 per cent), with a viable leg in 23 cases (74 per cent) at the time of patient discharge or death. There were five wound haematomas but no evidence of systemic fibrinolysis. Four amputations were required, none in the group undergoing successful lysis, and there were seven deaths, five from cardiac disease. Arteriography after balloon-catheter embolectomy is essential to detect residual thromboembolus and intraoperative streptokinase appears to be a safe and effective way of removing this.

Percutaneous intra-arterial thrombolysis is now well established for the treatment of acute leg ischaemia[1]. However, complete clot lysis may take many hours and so the technique is of little use when the limb is ischaemic to the extent that immediate intervention is required to save it. The treatment of choice in such circumstances remains thromboembolectomy using a balloon catheter[2,3]. Unfortunately, this procedure fails to reperfuse the leg in a significant proportion of cases, a failure that results in amputation or death[4–6]. One reason for this is incomplete clearance of thrombus; studies of intraoperative arteriography have shown this to occur in up to 30 per cent of patients[7,8]. A logical solution to this problem is to combine surgical embolectomy with intraoperative thrombolysis[9–11]. The aim of this prospective study was to see whether intraoperative streptokinase could lyse thrombus remaining after thromboembolectomy.

Patients and methods

Over a 3-year period, intraoperative thrombolysis was performed on 31 acutely ischaemic legs when intraoperative arteriography had demonstrated persistent occlusion after balloon-catheter thromboembolectomy. Figures for the total number of patients with acute leg ischaemia treated by embolectomy during this time are not available because not all surgeons at the relevant hospitals contributed to the study. However, operative arteriography was employed routinely by the participating surgeons and revealed persistent distal thrombus or occlusion in over one-third of patients.

There were 30 patients, 16 men and 14 women, aged 43–82 (median 73) years. The indication for operation was severe ischaemia with sensorimotor loss in 25 limbs, failed percutaneous thrombolysis in three and acute graft occlusion where the graft was not accessible for percutaneous thrombolysis in three. Preoperative arteriography was performed in only 16 patients.

The cause of ischaemia was probable primary embolism in nine legs (eight of cardiac origin, one from an aortic aneurysm), probable thrombosis in 11 (including two popliteal aneurysms), graft occlusion in five (one femorofemoral, one iliopopliteal, three femoropopliteal) and iatrogenic embolism in six (five following percutaneous angioplasty, one after aortic surgery). The distinction between primary embolism and thrombosis was made on the basis of preoperative risk factors (electrocardiographic evidence of arrhythmia or myocardial infarction, history of claudication, presence of contralateral pulses) and arteriographic, operative, histological and autopsy findings. A total of 21 perfemoral, 11 perpopliteal and four graft embolectomies were performed. The balloon catheters (2–4 Fr) were repeatedly passed distally until no further thromboembolic material could be retrieved.

Operative arteriography was then performed by placing a film cassette under the leg and infusing 10–20 ml contrast medium (usually Omnipaque; Nycomed, Birmingham, UK) via a Tibbs cannula or plastic catheter inserted into the arteriotomy and held in position with a Silastic (Dow Corning, Reading, UK) sling. After femoral exploration, the cannula was usually passed into the origin of the superficial femoral artery, but if this was occluded by existing atheroma then the arteriogram was obtained via the profunda femoris artery.

Once persistent distal thrombus or occlusion had been demonstrated, intraoperative thrombolysis was attempted. Streptokinase, 100 000 units in 100 ml normal saline, was infused over 30 min down the superficial femoral artery via the cannula used for the arteriogram. Thrombolysis after popliteal exploration was performed by infusing streptokinase into the distal popliteal artery or by divided doses down the individual tibial branches. No attempt was made to embed the catheter in the thrombus. Repeat arteriography was then performed to assess the degree of clot lysis. If this demonstrated incomplete lysis then a further attempt at embolectomy was made and another arteriogram obtained if more thrombus was retrieved.

Additional procedures depended largely on the degree of clot lysis on repeat arteriography. Nothing further was performed in 13 limbs and embolectomy was successfully repeated on three occasions. Operative transluminal balloon angioplasty of an underlying stenosis was performed in six cases. Two femoropopliteal below-knee vein grafts were necessary for persistent occlusion of the superficial femoral and

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popliteal arteries and one for a thrombosed popliteal aneurysm following a popliteal embolectomy. Two femorofemoral grafts and one iliopopliteal crossover reconstruction were required because of poor inflow. Anterior and posterior compartment fasciotomy of fascia and skin from knee to ankle was performed in three patients.

After operation all patients underwent anticoagulation with a heparin infusion according to the activated partial thromboplastin time (APTT). Peroperative coagulation profiles were not routinely obtained. Wound haematomas and other bleeding problems were recorded. A successful outcome was defined as complete or partial clot lysis on operative arteriography, restoration of pedal pulses and a viable leg at discharge or death. Preoperative and postoperative Doppler ankle artery pressure indices were obtained in 25 patients.

Results

On postembolectomy arteriography the popliteal artery was occluded in 11 cases, the tibial arteries in 14, the superficial femoral artery in four and the profunda femoris in two cases where there was existing occlusion of the superficial femoral artery. In most instances the level of occlusion corresponded to the point beyond which the embolectomy catheter could not be passed. Occlusion of the popliteal or tibial arteries was, however, found on eight occasions when the catheter had been passed to the ankle.

The arteriogram after streptokinase infusion demonstrated

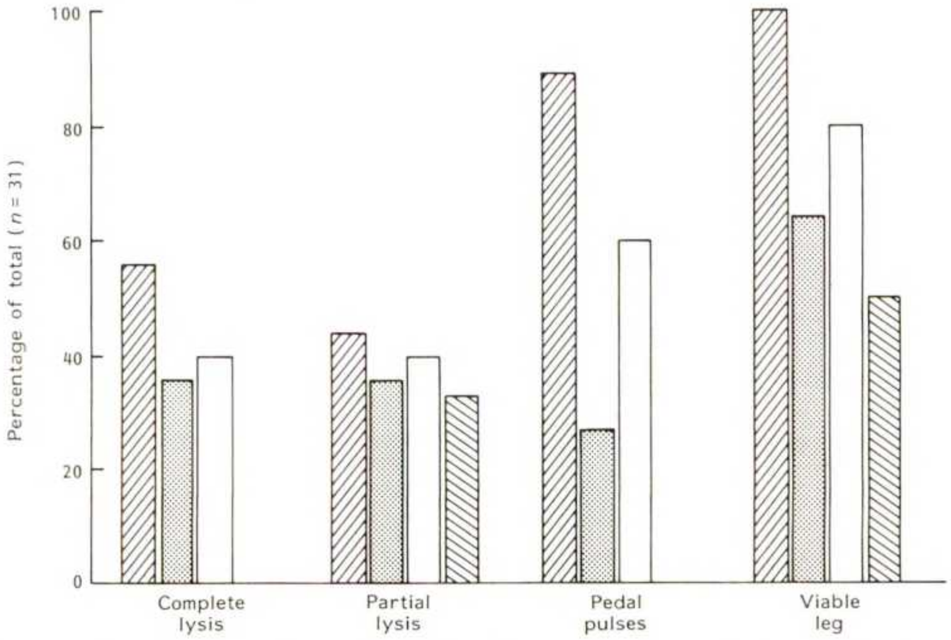

Figure 1 *Results of lysis according to the cause of ischaemia.* ▨, *Embolism* (n = *9*); ▒, *thrombosis* (n = *11*); □, *graft occlusion* (n = *5*); ▧, *iatrogenic embolism* (n = *6*)

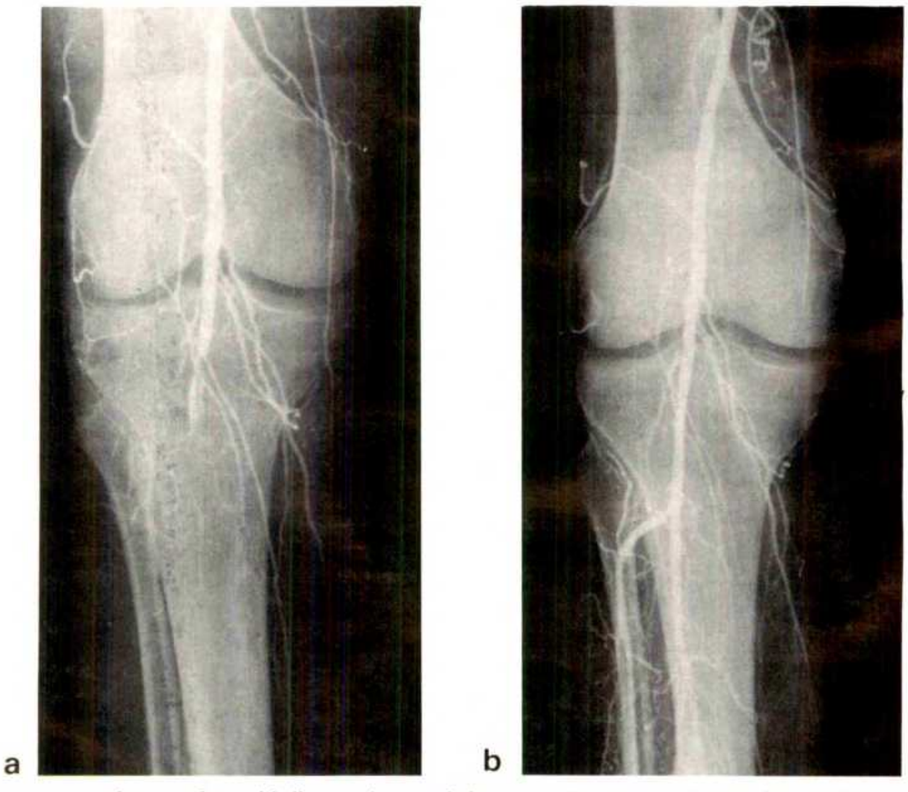

Figure 2 *Operative arteriograms after transfemoral balloon-catheter embolectomy.* **a** *Persistent occlusion of the popliteal artery despite the catheter passing to the ankle;* **b** *repeat arteriogram after streptokinase treatment showing complete lysis with three-vessel run-off*

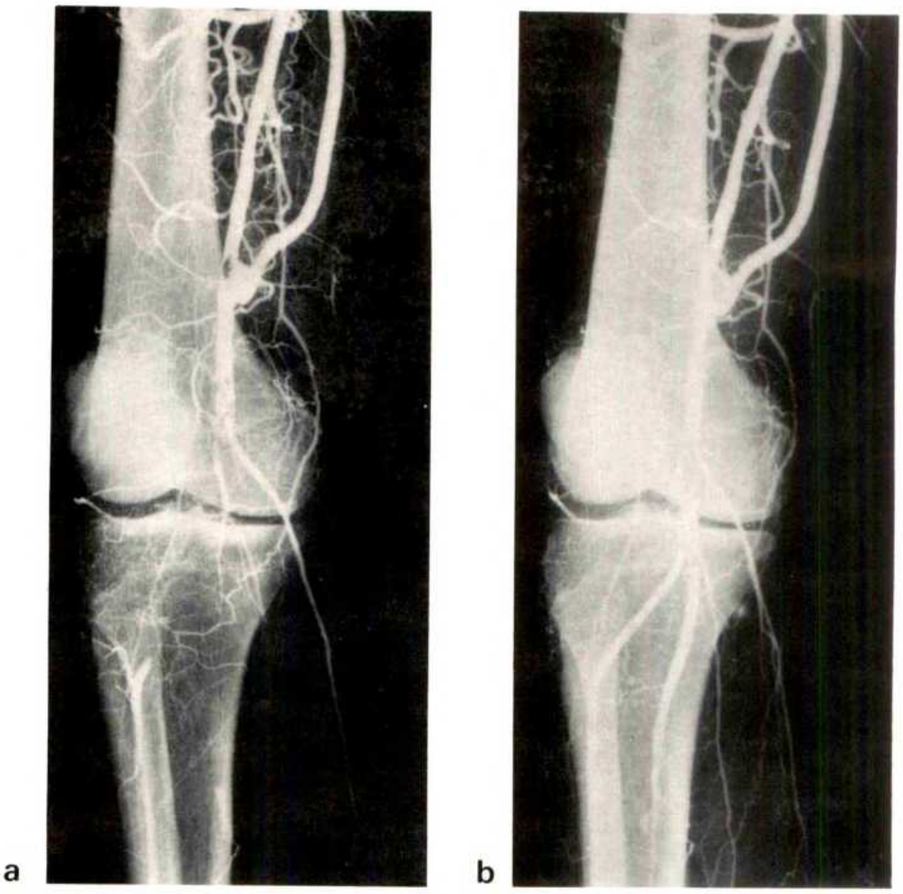

Figure 3 *Operative arteriograms after balloon-catheter thrombectomy of an above-knee polytetrafluoroethylene graft.* **a** *Good graft clearance but occlusion of the popliteal artery;* **b** *repeat arteriogram after streptokinase treatment showing almost complete lysis and revealing an underlying stenosis that was treated by angioplasty*

complete lysis in 11 legs (35 per cent), partial lysis in another 12 (39 per cent) and no change in eight (26 per cent). Of the eight that showed no change, the occlusion was found to result from atherosclerosis of the run-off rather than thrombus in five cases following popliteal exploration or autopsy. The other three were unproven, but there was not a single case of proven thrombus that was not at least partially lysed by streptokinase. After incomplete lysis, repeat embolectomy succeeded in clearing remaining thrombus from the popliteal artery on three occasions. After operation, at least one pedal pulse was restored in 14 limbs (45 per cent), and the leg was viable in 23 cases (74 per cent) at discharge or death. Doppler ankle pressure indices rose from a median of 0 (range 0–0·40) to 0·75 (range 0–1·05). There was a significant association (Fisher's exact test) between successful lysis and restoration of pedal pulses ($P = 0{\cdot}003$) and a similar correlation with leg viability ($P = 0{\cdot}014$).

The results subdivided according to the cause of ischaemia are summarized in *Figure 1*. The outcome for primary embolism was excellent with complete or partial lysis in all nine limbs, restoration of pedal pulses in eight and a viable leg in all cases (*Figure 2*). The results for thrombosis or graft occlusion were encouraging and much better if the problem was not caused by existing atherosclerosis of the run-off (*Figure 3*). Patients with iatrogenic emboli, which are often composed of atherosclerotic rather than thrombotic material, fared badly. Complete clot lysis never occurred and viability was achieved in only three of six legs. Embolectomy was repeated in four legs that rethrombosed due to poor run-off or atheromatous emboli, but none was salvaged.

There were five wound haematomas after operation but none required exploration; it should be noted that all patients received postoperative heparin anticoagulation. There were no bleeding problems in the three legs in which open fasciotomy had been performed. Full coagulation profiles were obtained in three patients with haematomas and although the APTT was raised there was no reduction in fibrinogen or platelet levels.

One patient developed a myocardial infarction 24 h after operation. It is possible that this was an extension of a subendocardial infarction that was the original source of the embolus. Two above-knee and two below-knee amputations were required, but none was in the group with successful lysis. There were seven deaths, five of which were cardiac in origin (three myocardial infarction, two heart failure). The other two were from bronchopneumonia following an above-knee amputation and a cerebral infarction 10 days after surgery.

Discussion

The technique of balloon-catheter embolectomy has changed little since its introduction by Fogarty *et al*. over 20 years ago[2]. Although it is a relatively simple method of rapidly removing arterial thrombus it is not without problems. With the advancing age of the population, underlying atherosclerosis may complicate the situation even if the cause is purely embolic, but increasingly acute thrombosis is the principal underlying problem[12]. Arterial damage by the catheter is more likely if atherosclerosis is present and this may also prevent distal passage of the catheter[13,14]. The latter also tends to enter the peroneal branch in preference to the anterior or posterior tibial artery[15]. Embolectomy is commonly performed 'blind' without radiological control despite several studies that have reported incomplete clearance of distal thrombus in up to 30 per cent of cases[7,8]. The results of embolectomy are also better when completion arteriography is performed[8,12]. The use of an end-hole balloon catheter passed over a guidewire may permit selective catheterization of the tibial arteries and repeated arteriography is also possible[16].

There have been several previous reports of intraoperative thrombolytic therapy[9–11] but this series is one of the largest yet reported and the first from the UK. In 1988, Norem *et al.*[9] reported the intraoperative use of boluses of streptokinase or urokinase in 26 legs to lyse residual thrombus following femoral embolectomy. All had angiographic evidence of clot lysis, with a viable leg in 85 per cent. Quinones-Baldrich and colleagues[10] reported the use of intraoperative infusion of streptokinase or urokinase in 23 legs with success in 74 per cent. Cohen *et al.*[11] used streptokinase in 11 legs after passing a catheter down into the clot, with success in 64 per cent. More recently, the same group[17] has reported improved results with tissue plasminogen activator (tPA) and this has also been used successfully on a small number of patients at St George's Hospital, London. Comerota *et al.*[18] have described a technique of isolated limb perfusion using 10^6 units urokinase infused into the occluded arteries, accompanied by popliteal venous drainage to reduce the systemic effect of such a high dose.

Streptokinase was chosen for the present study as it was easily obtainable and inexpensive compared with urokinase or tPA. Lower clot lysis times have been reported for tPA than for streptokinase in percutaneous thrombolysis[19], but overall lysis rates are similar and the high cost of tPA is difficult to justify at present. There is probably an indication for tPA in patients who have received streptokinase within the previous year as they are likely to have high antibody levels that will inactivate further doses and may cause anaphylaxis[20]. The dose of 100 000 units was selected because the literature suggested that this was unlikely to be associated with significant bleeding[1,9–11,18].

There were no operative problems due to excessive bleeding, even after open fasciotomy. Although there were five wound haematomas, all patients were receiving heparin. In the three patients for whom coagulation profiles were obtained, there was no fall in fibrinogen or platelet levels to suggest significant systemic fibrinolysis. A 30-min infusion was used because of concern that a bolus would gradually leach out of the distal arterial tree even though it was isolated. No attempt was made to embed the catheter in the clot[21] as this would have increased the technical difficulty of the procedure. It was, in any case, thought to be unnecessary because of the lack of blood flow.

Good lysis was obtained if the distal occlusion was caused by thrombus or embolus of thrombotic origin. As might be expected, streptokinase made little impact on poor run-off due to existing atherosclerotic occlusion. However, arteriographic differentiation was often difficult and the diagnosis was revealed only after popliteal exploration or at subsequent autopsy. It is likely that popliteal exploration was avoided in cases of successful lysis following femoral embolectomy. Popliteal embolectomy with exposure of the origin of all three calf vessels is a technically demanding procedure that may require conversion from local to general anaesthesia in the high-risk patient[22].

The disappointing results of lysis following iatrogenic embolism were probably caused by the atheromatous composition of the emboli. Streptokinase was able to lyse the propagated thrombus but, if cholesterol microembolism had occurred, tissue perfusion was not improved and rethrombosis supervened[23]. Histological examination after skin biopsy, amputation or autopsy in three of the six cases confirmed cholesterol embolism.

Although the overall limb salvage rate of 74 per cent was encouraging, there were five deaths of cardiac origin. All but one of these was from exacerbation of a premorbid condition that was probably the original cause of the acute leg ischaemia. The high incidence of cardiac death reflects the increasing incidence of ischaemic heart disease in these patients[12,24] and is probably unavoidable. What should now be avoidable, in most cases, is death or amputation resulting from inadequate reperfusion of an acutely ischaemic leg.

In summary, it is felt that arteriography to detect residual thromboembolus following balloon-catheter embolectomy is essential. Intraoperative streptokinase appears to be a safe and effective method of lysing persistent thrombus; its use may avoid the need for more distal exploration.

References

1. Earnshaw JJ. Thrombolytic therapy in the management of acute limb ischaemia. *Br J Surg* 1991; **73**: 261–9.
2. Fogarty TJ, Daily PO, Shumway NE, Krippachne W. Experience with balloon catheter technique for arterial embolectomy. *Am J Surg* 1971; **122**: 231–7.
3. Blaisdell FW, Steele M, Allen RE. Management of acute lower extremity arterial ischaemia due to embolism and thrombosis. *Surgery* 1978; **84**: 822–34.
4. Jivegard L, Holm J, Schersten T. The outcome of arterial embolism. *Acta Chir Scand* 1986; **152**: 251–6.
5. Dregelid EB, Stangeland LB, Eide GE, Trippestaed A. Patient survival and limb prognosis after arterial embolectomy. *Eur J Vasc Surg* 1987; **1**: 263–71.
6. Murie JA, Mathieson M. Arterial embolectomy in the leg: results in a referral hospital. *J Cardiovasc Surg (Torino)* 1987; **28**: 184–8.
7. Mavor GE, Walker MG, Dhall DP. Routine operative arteriography in arterial embolectomy. *Br J Surg* 1972; **59**: 482–4.
8. Bosma HW, Jorning PJG. Intraoperative arteriography in arterial embolectomy. *Eur J Vasc Surg* 1990; **4**: 469–72.
9. Norem RF, Short DH, Kerstein MD. Role of intraoperative fibrinolytic therapy in acute arterial occlusion. *Surg Gynecol Obstet* 1988; **167**: 87–91.
10. Quinones-Baldrich WJ, Baker D, Busuttil RW, Machleder HI. Intraoperative infusion of lytic drugs for thrombotic complications of revascularization. *J Vasc Surg* 1989; **10**: 408–17.
11. Cohen H, Kaplan M, Bernhard VM. Intraoperative streptokinase. An adjunct to mechanical thrombectomy in the management of acute ischaemia. *Arch Surg* 1986; **121**: 708–15.
12. Englund R, Magee HR. Peripheral arterial embolism: 1961–1985. *Aust N Z J Surg* 1987; **57**: 27–31.
13. Foster JH, Carter JW, Graham CP, Edwards WH. Arterial injuries secondary to the use of the Fogarty catheter. *Ann Surg* 1970; **171**: 971–8.
14. Byrnes G, MacGowan WA. The injury potential of the Fogarty balloon catheters. *J Cardiovasc Surg (Torino)* 1975; **175**: 590–3.
15. Short D, Vaughn GD, Jachimczyk J *et al.* The anatomic basis for the occasional failure of transfemoral balloon catheter thromboembolectomy. *Ann Surg* 1979; **190**: 555–6.
16. Robiczek F. Dye-enhanced fluoroscopy-directed catheter embolectomy. *Surgery* 1984; **95**: 622–4.
17. Parent FN, Bernhard VM, Pabst TS, McIntyre KE, Hunter GC, Malone JM. Fibrinolytic treatment of residual thrombus after catheter embolectomy for severe lower limb ischaemia. *J Vasc Surg* 1989; **9**: 153–60.
18. Comerota AJ, White JV, Grosh JD. Intra-operative intra-arterial thrombolytic therapy for salvage of limbs in patients with distal arterial thrombosis. *Surg Gynecol Obstet* 1989; **169**: 283–9.
19. Berridge DC, Gregson RHS, Hopkinson BR, Makin GS. Randomized trial of intra-arterial recombinant tissue plasminogen activator, intravenous tPA and intra-arterial streptokinase in peripheral arterial thrombolysis. *Br J Surg* 1991; **78**: 988–95.
20. Jalihal S, Morris GK. Antistreptokinase titres after intravenous streptokinase. *Lancet* 1990; **335**: 184–5.
21. Dotter CJ, Rosch J, Seaman AJ. Selective clot lysis with low dose streptokinase. *Radiology* 1974; **111**: 31–7.
22. Abbott WM, Maloney RD, Wirthlin LS. Embolism of the popliteal artery. *Surg Gynecol Obstet* 1984; **159**: 533–6.
23. Gaines PA, Kennedy A, Moorhead P, Cumberland DC, Welsh CL, Rutley MS. Cholesterol embolisation: a lethal complication of vascular catheterisation. *Lancet* 1988; **i**: 168–70.
24. Clason AE, Stonebridge PA, Duncan AJ, Nolan B, Jenkins AM, Ruckley CV. Morbidity and mortality in acute lower limb ischaemia: a 5-year review. *Eur J Vasc Surg* 1975; **175**: 590–3.

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Choice of agent for peripheral thrombolysis

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Evidence has been accumulating that tissue plasminogen activator (tPA) is a more rapid and effective agent than streptokinase for peripheral thrombolysis. Twenty-three patients with acute limb-threatening ischaemia treated with tPA (0·5 mg h^{-1}*) over 15 months were compared with 20 consecutive patients previously receiving streptokinase (5000–10 000 units* h^{-1}*). There were no major differences between the rates of complete and partial lysis (61 per cent for tPA* versus *65 per cent for streptokinase) or limb salvage (65* versus *55 per cent respectively). Complication rates were also similar. It was not possible to show that tPA, an agent ten times more expensive than streptokinase, was superior for peripheral thrombolysis.*

High-dose intravenous streptokinase has been used for 30 years in the treatment of acute limb ischaemia[1–3]. However, poor clinical results, a high incidence of haemorrhagic complications and the introduction of the Fogarty embolectomy catheter ensured that surgery became the principal treatment for this condition. The development of local low-dose thrombolytic therapy significantly improved results and low-dose intra-arterial streptokinase became the 'gold standard' non-surgical treatment for acute limb ischaemia[4].

The activation of plasminogen produced by streptokinase is not specific to abnormal thrombus. The high incidence of haemorrhagic complications, associated particularly with high-dose intravenous streptokinase, is related to the breakdown of plasma fibrinogen. In the past decade new thrombolytic agents have been developed that bind specifically to fibrin and act only at the site of abnormal thrombus. Two such fibrin-specific agents are in clinical use: an acylated complex of streptokinase and plasminogen, anistreplase (Eminase; SmithKline Beecham Pharmaceuticals, Welwyn Garden City, UK), and tissue plasminogen activator (tPA) (Actilyse; Boehringer Ingelheim, Bracknell, UK).

Recent retrospective reports on intra-arterial thrombolysis have suggested that tPA is faster and more effective than streptokinase[5–8]. In the only randomized trial to date, which included 40 patients, successful lysis and limb salvage rates were higher with tPA than streptokinase[9]. Although much of the available evidence is from uncontrolled studies, tPA has been endorsed for peripheral thrombolysis[10].

In this unit, peripheral thrombolysis has been available since 1985 and results for the first 3 years have been published[11]. The unit presently has experience of over 100 cases. In response to the accumulating evidence, streptokinase was replaced by tPA in 1989. The cost of 24 h of treatment with tPA is more than ten times that of streptokinase[4]. The aim of the present study was to examine whether changing to tPA improved the clinical results of peripheral thrombolysis and justified the additional expense.

Patients and methods

Embolectomy was reserved for patients with a short duration of limb ischaemia, no previous history of claudication and a clinically obvious source of embolism[12]. Other patients with acute limb ischaemia underwent urgent arteriography followed by thrombolytic therapy unless the limb was so severely ischaemic that emergency surgery was required. Some patients with acute critical ischaemia including a neurological deficit were still candidates for lysis if no distal vessels were outlined for surgical bypass.

Between April 1990 and June 1991, 23 patients with acute limb-threatening ischaemia received intra-arterial tPA at 0·5 mg h^{-1}. In a similar 15-month period before this, a total of 20 patients received low-dose intra-arterial streptokinase: ten had 5000 and ten 10 000 units h^{-1} (*Table 1*). All but one patient had a femoropopliteal occlusion; the causes of ischaemia are shown in *Table 2*. The catheter advancement technique used has previously been described[11]. Patients were treated on the surgical wards but returned to the radiology department at intervals of a maximum of 12 h for angiography and catheter adjustment as required. A median of 2 (range 1–8) visits to the radiology department were required.

Results

The median duration of lysis was 18 h for streptokinase and 22 h for tPA. There was no difference between the duration of lysis in successful or failed cases, or at the different streptokinase doses. Successful lysis, defined as restoration of distal pulses with angiographic evidence of clot clearance, occurred at a

Table 1 *Patient details*

	Streptokinase	Tissue plasminogen activator
No. of patients	20	23
Sex ratio (M:F)*	15:5 (75:25)	15:8 (65:35)
Median (range) age (years)	70 (28–82)	66 (52–84)
Hypertension*	6 (30)	5 (22)
Coronary artery disease*	6 (30)	7 (30)
Cerebrovascular disease*	3 (15)	3 (13)
Acute critical ischaemia (neurosensory loss)*	5 (25)	9 (39)
Median (range) duration of ischaemia (days)	1 (1–14)	3 (1–28)

*Values in parentheses are percentages

Table 2 *Cause of ischaemia*

	Streptokinase (*n* = 20)	Tissue plasminogen activator (*n* = 23)
Thrombosis	8 (40)	12 (52)
Embolism	0 (0)	2 (9)
Graft thrombosis	2 (10)	5 (22)
After angioplasty	9 (45)	3 (13)
After embolectomy	1 (5)	0 (0)
After angiography	0 (0)	1 (4)

Values in parentheses are percentages

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Table 3 *Results*

	Streptokinase ($n = 20$)	Tissue plasminogen activator ($n = 23$)
Lysis		
Complete	11 (55)	10 (43)
Partial	2 (10)	4 (17)
Failed	7 (35)	9 (39)
Outcome at 30 days		
Limb salvage	11 (55)	15 (65)
Amputation	7 (35)	4 (17)
Death	2 (10)	4 (17)

Values in parentheses are percentages

Table 4 *Complications*

	Streptokinase ($n = 20$)	Tissue plasminogen activator ($n = 23$)
Catheter-related	2 (10)	1 (4)
Haemorrhage		
Minor	3 (15)	2 (9)
Major	3 (15)	5 (22)
Early rethrombosis	1 (5)	0 (0)
Major vascular reconstruction	7 (35)	10 (43)

Values in parentheses are percentages

similar rate for tPA (43 per cent) and streptokinase (55 per cent) (*Table 3*). In addition, clinically useful partial lysis was observed in six patients: four receiving tPA and two streptokinase. For example, lysis in the run-off of a thrombosed popliteal aneurysm enabled bypass surgery to be performed. Ten vascular surgical procedures were performed in the 16 patients in whom lysis failed; six operations resulted in limb salvage. After successful lysis, two patients in each group underwent angioplasty and seven had vascular reconstructions.

Limb salvage rates for tPA (65 per cent) and streptokinase (55 per cent) were similar. This rate was reduced in patients with acute critical ischaemia including a neurological deficit: only three patients (21 per cent) had successful lysis, limb salvage being achieved in six (43 per cent). The highest rate of both successful lysis (61 per cent) and limb salvage (69 per cent) occurred in the 12 patients treated after early thrombosis of a successful angioplasty.

Complications were frequent (*Table 4*). Three patients had catheter-related problems: either the catheter was inadvertently removed or the infusion switched off, usually owing to inexperience on the ward. Major haemorrhage requiring cessation of treatment occurred in five patients receiving tPA (22 per cent) and three given streptokinase (15 per cent). Urgent surgery was necessary in three patients receiving tPA. One had a retroperitoneal haemorrhage that proved fatal despite exploration. The other two patients required surgery for an enlarging groin haematoma, one of which developed in a hernia sac for which orchidectomy was needed during repair.

Discussion

Hopes were raised that fibrin-specific thrombolytic agents given intravenously would improve on results with intravenous streptokinase, using which approximately 30 per cent of patients with acute limb ischaemia had successful lysis[1–3]. However, studies using intravenous anistreplase for acute limb ischaemia gave similar results[13]. In the third arm of a randomized trial comparing intra-arterial streptokinase and tPA, 20 patients treated with the latter intravenously had a rate of complete lysis of only 30 per cent[9]. Despite the ease of intravenous thrombolytic treatment, none of the agents given this way has produced results comparable to those of intra-arterial streptokinase.

The results of the present intra-arterial lysis programme are similar to those previously reported[11] and fall within the accepted range[4]. There appears to be no advantage in using tPA instead of streptokinase. Others have, however, achieved superior results with tPA, reporting lysis rates from 62 to 93 per cent and limb salvage rates of 80–94 per cent[5–8]. It has been stated that tPA has a speedier action than streptokinase, although in this study the duration of lysis was not reduced by tPA, even if patients with failed lysis are excluded[8,9]. A difference between this and other studies is that the median duration of ischaemia (1 day) in Bristol was considerably shorter[8,9]. Results with thrombolysis are superior in patients with stable acute ischaemia. In addition, this study included relatively few patients with graft thrombosis, a condition for which the outcome from thrombolysis is much less certain. One reason for the reported advantages of tPA may be that most studies of thrombolysis are retrospective and sequential; lessons learned using streptokinase treatment may have improved subsequent results with tPA.

Several possible explanations for the apparent lack of superiority of tPA in this unit have been identified. Although it was thought that the indications for thrombolysis were unchanged, more patients with acute thromboses and fewer with postangioplasty thrombosis received tPA in the second part of the study (*Table 2*). The former have a low rate of complete lysis and the latter a high rate. In addition, more patients receiving tPA had acute critical ischaemia with a neurological deficit, a factor known to cause a poor outcome[14]. These problems highlight the difficulties of interpreting non-randomized studies[15].

Conclusive evidence of the superiority of tPA over streptokinase is still lacking. It remains questionable whether fibrin specificity confers any benefit in intra-arterial thrombolysis either by enhancing lytic activity or by reducing complications[16]. This is the case in coronary thrombolysis, where neither tPA nor anistreplase has been shown to have any advantage over streptokinase in the recent International Study of Infarct Survival Collaborative Group report of 42 000 patients[17]. Unless new evidence emerges, it is arguable whether other new expensive fibrin-specific agents will produce better outcomes. Perhaps clinical research in peripheral thrombolysis should concentrate on the development of safe effective regimens with low-dose streptokinase[18] and on new physical methods of speeding clot lysis such as lacing, mechanical disruption or pulse-spray lysis[19–21].

Alternatively, other methods such as high-dose bolus infusion may speed lysis. This has recently been described using tPA but has not been tried with streptokinase[22]. Broad experience with thrombolysis is still lacking and there is a major need for multicentre trials. The Thrombolysis Study Group has recently formed in the UK and a large trial comparing tPA with streptokinase should be foremost on its agenda to determine whether the high costs of tPA are justified by improved results. This should help prevent a situation similar to the recent 'battle of the (coronary) clotbusters'[23].

Ultimately, the price of lytic agents may assume little importance in the overall cost of treating acute limb ischaemia as the duration of hospital stay is the key determinant. Future studies will need to include a cost–benefit analysis of thrombolysis in a similar way to that undertaken for femorodistal bypass[24].

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References

1. Amery A, Deloof W, Vermylen J, Verstraete M. Outcome of recent thromboembolic occlusions of limb arteries treated with streptokinase. *BMJ* 1970; iv: 639–44.

2. Fiessinger JN, Aiach M, Vayssairat M, Juillet Y, Cormier JM, Houssett E. Traitment thrombolytique des arteriopathies. *Annals Anaesthesia Français* 1978; **19**: 739–45.
3. Earnshaw JJ, Cosgrove C, Wilkins DC, Bliss BP. Acute limb ischaemia: the place of intravenous streptokinase. *Br J Surg* 1990; **77**: 1136–9.
4. Earnshaw JJ. Thrombolytic therapy in the management of acute limb ischaemia. *Br J Surg* 1991; **78**: 261–9.
5. Graor RA, Risius B. Thrombolysis with recombinant human tissue-type plasminogen activator in patients with peripheral artery and bypass graft thrombosis. In: Sobel BE, Collen D, Grossbard EB, eds. *Tissue Plasminogen Activator in Thrombolytic Therapy*. New York: Dekker, 1987: 171–204.
6. Berridge DC, Gregson RHS, Makin GS, Hopkinson BR. Tissue plasminogen activator in peripheral arterial thrombolysis. *Br J Surg* 1990; **77**: 179–82.
7. Dawson K, Reddy K, Platts AD, Hamilton G. Results of a recently instituted programme of thrombolytic therapy in acute lower limb ischaemia. *Br J Surg* 1991; **78**: 409–11.
8. Lonsdale RJ, Berridge DC, Earnshaw JJ *et al.* Recombinant tissue plasminogen activator is superior to streptokinase for local intra-arterial thrombolysis. *Br J Surg* 1992; **79**: 272–5.
9. Berridge DC, Gregson RHS, Hopkinson BR, Makin GS. Randomized trial of intra-arterial recombinant tissue plasminogen activator, intravenous recombinant tissue plasminogen activator and intra-arterial streptokinase in peripheral arterial thrombolysis. *Br J Surg* 1991; **78**: 988–95.
10. Hess H. Thrombolytic therapy in peripheral vascular disease. *Br J Surg* 1990; **77**: 1083–4.
11. Scott DJA, Wyatt MG, Wilson YG, Murphy P, Baird RN, Horrocks M. Intra-arterial streptokinase infusion in acute lower limb ischaemia. *Br J Surg* 1991; **78**: 732–4.
12. Scott DJA, Davies AH, Horrocks M. Risk factors in selected patients undergoing femoral embolectomy. *Ann R Coll Surg Engl* 1989; **71**: 229–32.
13. Earnshaw JJ, Westby JC, Makin GS, Hopkinson BR. Low dose intra-arterial streptokinase and acylated plasminogen–streptokinase activator complex: a retrospective review of two thrombolytic regimes in recent peripheral arterial ischaemia. *Eur J Vasc Surg* 1987; **1**: 151–8.
14. Earnshaw JJ, Hopkinson BR, Makin GS. Acute critical ischaemia: a prospective evaluation. *Eur J Vasc Surg* 1990; **4**: 365–8.
15. Allen DR, Smallwood J, Johnson CD. Intra-arterial thrombolysis should be the initial treatment of the acutely ischaemic limb. *Ann R Coll Surg Engl* 1992; **74**: 106–11.
16. Berridge DC, Makin GS, Hopkinson BR. Local low dose intra-arterial thrombolytic therapy: the risk of stroke or major haemorrhage. *Br J Surg* 1989; **76**: 1230–3.
17. Third International Study of Infarct Survival Collaborative Group. ISIS-3: a randomized comparison of streptokinase *vs* tissue plasminogen activator *vs* anistreplase and of aspirin plus heparin *vs* aspirin alone among 41 299 cases of suspected myocardial infarction. *Lancet* 1992; **339**: 753–70.
18. Walker WJ, Giddings AEB. A protocol for the safe treatment of acute lower limb ischaemia with intra-arterial streptokinase and surgery. *Br J Surg* 1988; **75**: 1189–92.
19. Sullivan K, Gardiner GA, Shapiro MJ, Bonn J, Levin DC. Acceleration of thrombolysis with high dose trans-thrombus bolus technique. *Radiology* 1989; **173**: 805–8.
20. Starke EE, McDermott JC, Crummy AB, Turnipseed WD, Archer CW, Burgess JH. Percutaneous aspiration thromboembolectomy. *Radiology* 1985; **156**: 51–6.
21. Bookstein JJ, Fellmeth B, Roberts A, Valji K, Davis G, Machado T. Pulsed-spray pharmacomechanical thrombolysis. *AJR Am J Roentgenol* 1989; **152**: 1097–100.
22. Buckenham TM, George CD, Chester JF, Taylor RS, Dormandy JA. Accelerated thrombolysis using pulsed intra-thrombus recombinant human tissue type plasminogen activator (t-PA). *Eur J Vasc Surg* 1992; **6**: 237–40.
23. O'Donnell M. Battle of the clotbusters. *BMJ* 1991; **302**: 1259–61.
24. Cheshire NJ, Noone MA, Davies L, Drummond M, Wolfe JHN. Economic options and decision making in the ischaemic lower limb. *Br J Surg* 1991; **78**: A371.

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Myocardial infarction after reconstruction of the abdominal aorta

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The records of 555 patients who underwent elective abdominal aortic reconstruction were analysed to identify risk factors predisposing to cardiac complications. Perioperative myocardial infarction occurred in 35 patients (6·3 per cent), of whom 12 (2·2 per cent) died. Using multiple logistic regression, four preoperative factors that were independently predictive for postoperative myocardial infarction were identified with the following relative risk ratios: history of transient ischaemic attacks, 5·08; raised serum creatinine level, 3·66; age >60 years, 3·00; and angina requiring regular treatment, 2·74. A scoring system using these four factors was devised that identified 150 of the 555 patients as at high risk, and included 69 per cent of those with myocardial infarction after operation and 83 per cent of those who died. A clinical risk score is a practical first step in identifying patients at risk of myocardial infarction; it would also reduce the number of patients for whom sophisticated tests of cardiac function were necessary.

When a surgeon advises a patient that surgery is necessary, the probability that the proposed operation will produce a long-lasting improvement must be balanced against the possibility that the patient may die during or after the operation or may suffer unacceptable complications. When operation on the infrarenal aorta and its iliac branches is considered, it is known from the literature that the mortality rate is 2–8 per cent, and that the principal cause of death is myocardial infarction[1–5]. Often there is no history or signs of ischaemic heart disease but one series in which all patients underwent coronary angiography before operation showed that more than two-thirds had covert heart disease[6]. This led to the proposition that all patients on whom it was intended to operate for aortic abdominal aneurysm (AAA) should undergo coronary angiography and coronary artery bypass when necessary[7,8]. It is reasonable that all patients scheduled for operation on the abdominal aorta should be screened for ischaemic heart disease, but there is debate about which tests of myocardial function to use – exercise electrocardiography, dipyridamole–thallium scanning, multiple-uptake gated acquisition scanning, measurement of ejection fraction or coronary angiography[3,8–14]. An alternative strategy is to select patients for these more sophisticated tests of cardiac function on the basis of clinical information and electrocardiography. If selective screening is to be effective one must know which clinical factors indicate increased risk of postoperative myocardial infarction. Several indices of risk have been devised but none has gained universal acceptance[15,16]. If patients at risk could be identified reliably, only a proportion of the total would require sophisticated tests of cardiac function, with a considerable saving in time and expense.

To answer these questions information was recorded from 555 consecutive patients who had operations to replace the abdominal aorta. Data were analysed to identify risk factors predicting postoperative myocardial infarction.

Patients and methods

Information was recorded from 555 consecutive patients undergoing aortic surgery (aortoiliac, aortobifemoral and aortic tube grafts) between January 1986 and December 1989. Only those who had an elective or urgent operation (e.g. for symptomatic aneurysm or pregangrene) were included; all emergency operations were excluded. The indications for operation were claudication, rest pain or pregangrene, and AAA. A detailed history and physical examination, routine blood biochemistry and haematology, a chest radiograph and a resting 12-lead electrocardiogram (ECG) were obtained for each patient. All preoperative factors that might influence the outcome of operation were studied; these included age, sex, primary diagnosis (whether aneurysm or occlusive arterial disease), history of coronary artery disease (including congestive heart failure and dysrhythmia), cerebrovascular disease, obstructive airway disease, hypertension, diabetes and smoking. Abnormalities on physical examination, electrocardiography, chest radiography and blood biochemistry were recorded. Patients suspected of having severe coronary artery disease were referred for further assessment to a cardiologist. On the basis of an examination, the cardiologist carried out sophisticated tests of myocardial function, echocardiography, exercise electrocardiography, dipyridamole–thallium scanning and coronary angiography.

Patients assessed by the cardiologists fell into four clinical categories: (1) considered to be at very high risk and hence unsuitable for surgery (such patients are not considered again in this analysis); (2) potential improvement with medical treatment; (3) recommended for coronary artery bypass surgery; and (4) considered to be at high risk but the indication for surgery outweighed all other considerations (painful and tender aneurysm, pregangrene or gangrene). The consultant anaesthetist was the final arbiter of who was or was not operated on. He did not decline to anaesthetize any patient in categories 2–4 who came through this process of selective screening.

To avoid as many variables as possible, all operations were performed by the same surgeon and anaesthetist. Anaesthesia was induced with thiopentone and maintained with halothane and nitrous oxide. During operation pulse rate, blood pressure, ECG, oxygen saturation, partial pressure of carbon dioxide, central venous pressure and urine output were monitored. Swan–Ganz catheters were not used. Operations were performed through a transverse incision and transperitoneal approach. An end-to-end anastomosis was virtually always used proximally and either end-to-end anastomosis to the common iliac arteries or end to side to the common femorals. The mean(s.d.) time of operation was 45(10) min with a mean total anaesthesia time of 55 min.

The principles adopted were: (1) to maintain blood pressure at the patient's usual level throughout operation; (2) to keep operation time and, in particular, clamp time to a minimum; and (3) to avoid blood loss and give blood rather than plasma expanders after operation (to minimize, where possible, pulmonary oedema and acute respiratory distress syndrome). After operation all patients spent 1–2 h in the recovery room and then returned to the ward. The vast majority were able to sit out of bed the following day and, other than at operation, patients were not ventilated. Nasogastric suction was not used unless

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the patient had prolonged ileus, which was rare, affecting only seven patients. The principle of ward management was to keep the systemic blood pressure at a level normal for the individual and to maintain the central venous pressure at 10 cm saline. Episodes of dysrhythmia, congestive cardiac failure, left ventricular failure and infarction (confirmed by changes in the isoenzymes, ECG or at autopsy) were classified as cardiac events. All such events within 30 days of operation were considered to be relevant.

Results

Of the 555 patients included in the study, 431 were men and 124 women (male:female ratio 3·5:1). In all, 351 (63·2 per cent) were operated on for aortic aneurysm and 204 (36·8 per cent) for aortoiliac occlusive disease. Of the 351 patients with aortic aneurysm, 76 had a tube graft (63 in category 2, 12 in category 3 and one in category 4). A total of 211 patients (38·0 per cent) had a history of coronary artery disease, including two with recent (<6 months) myocardial infarction (*Table 1*). The incidence of additional risk factors in these patients was not significantly different from that in the entire series (*Table 2*). In all, 460 patients were thought to be fit for surgery with minimal risk of postoperative myocardial infarction and were operated on without being seen by a cardiologist.

The remaining 95 underwent operation after being seen by a cardiologist and fell into categories 2–4: in category 2, 62 patients were operated on after they had responded to medical management; in category 3, 23 who had had a coronary artery bypass as a result of cardiological investigation later had aortic surgery; and in category 4, ten were operated on in spite of high risk for over-riding surgical reasons.

Thirty-five confirmed myocardial infarctions occurred within 30 days of operation, an incidence of 6·3 per cent. Twelve patients died from a cardiac complication, all of them myocardial infarcts (2·2 per cent). The incidence of infarction was 5·7 per cent in patients considered to be at low risk and 9·5 per cent in the high-risk group referred for cardiological assessment (*Table 3*). Arrhythmia occurred in 40 patients, making it the most common complication if short-lasting intraoperative arrhythmias are included; 24 were ventricular.

Four patients had an intraoperative myocardial infarction. Nineteen infarcts occurred within 48 h of surgery (*Figure 1*). Ten additional patients suffered infarction within the first week after operation. Ten of the 12 fatal infarcts occurred within the first 48 h of surgery. There were eight deaths in the 460 patients who were operated on and were thought to be at low risk, and four in the higher risk group of 95 patients. The difference in incidence of myocardial infarction between the low- and high-risk groups was not statistically significant ($P = 0{\cdot}12$, Fisher's exact test), nor was there a significant difference in the number of fatal infarcts between the two groups ($P = 0{\cdot}13$, Fisher's exact test).

The incidence of infarction in category 3 patients was 4 per cent and it is arguable that after coronary artery bypass these patients would be more appropriately classified as low risk. When category 3 patients are included in the low-risk group and compared with groups 2 and 4, there is again no significant difference in the incidence of cardiac complications between them.

Because there was no significant difference in the incidence of myocardial infarction between the high- and low-risk groups, it was clear that some patients at risk were being missed and that a more structured approach to selection was necessary. In retrospect, and based on the data acquired, each patient was assigned a cardiac risk class based on the Goldman multifactorial index[15]. Goldman and colleagues studied 1001 patients who were scheduled to have operations including emergencies. They correlated cardiac outcome with each variable by univariate analysis, and then used multivariate

Table 1 *Preoperative characteristics of 555 patients*

	No. of patients
Ischaemic heart disease	211 (38·0)
Angina	142 (25·6)
Myocardial infarction	138 (24·9)
Left ventricular failure	27 (4·9)
Cardiac arrhythmia	15 (2·7)
Hypertension	173 (31·2)
Diabetes	39 (7·0)
Cerebrovascular disease	77 (13·9)
Transient ischaemic attacks	45 (8·1)
Stroke	36 (6·5)
Obstructive airway disease	109 (19·6)
Smokers	521 (93·9)
Past	247 (44·5)
Present	274 (49·4)
Disordered renal function	48 (8·6)

Values in parentheses are percentages

Table 2 *Additional risk factors in 211 patients with ischaemic heart disease*

	No. of patients
Hypertension	84 (39·8)
Diabetes	19 (9·0)
Smoking	197 (93·4)
Past	100 (47·4)
Present	97 (46·0)
Cerebrovascular disease	27 (12·8)
Obstructive airway disease	36 (17·1)
Disordered renal function	22 (10·4)

Values in parentheses are percentages

Table 3 *Cardiac complications in 555 patients*

	No. of patients
Cardiac complications	70 (12·6)
Myocardial infarction	35 (6·3)
Not seen by cardiologist ($n = 460$)	26 (5·7)
Seen by cardiologist ($n = 95$)	9 (9·5)
Fatal infarctions	12 (2·2)
Arrhythmia	40 (7·2)
Atrial	16 (2·9)
Ventricular	24 (4·3)
Left ventricular failure	23 (4·1)
Myocardial infarction and arrhythmia	18 (3·2)
Myocardial infarction and left ventricular failure	10 (1·8)
Cardiac death	12 (2·2)
Myocardial infarction	12
Ventricular fibrillation	5
Left ventricular failure	4
Cardiogenic shock	4
Renal failure	3

Values in parentheses are percentages

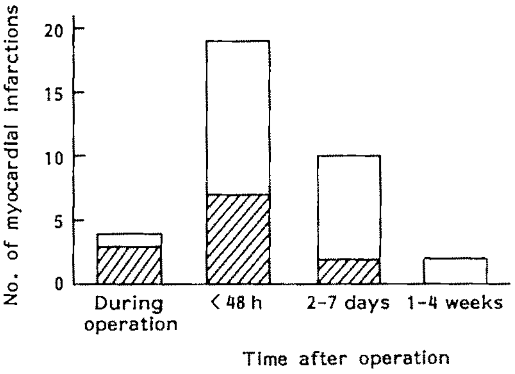

Figure 1 *Incidence of non-fatal* (□) *and fatal* (■) *myocardial infarctions during and after aortic surgery*

Table 4 *Association of Goldman's cardiac risk index classification with postoperative myocardial infarction*

Goldman class	No. of patients	No. of infarcts	No. of deaths
1	333 (60·0)	17 (5·1)	4 (1·2)
2	179 (32·3)	13 (7·3)	6 (3·4)
3	37 (6·7)	5 (14)	2 (5)
4	6 (1·1)	0 (0)	0 (0)

Values in parentheses are percentages

Table 5 *Risk factors for myocardial infarction following aortic surgery*

Factor	Relative risk	*P*
Age >60 years	3·32 (1·13–9·75)	0·011
History of angina	2·32 (1·14–4·73)	0·021
History of congestive cardiac failure	3·77 (1·31–10·90)	0·025
History of transient ischaemic attacks	3·87 (1·62–9·26)	0·005
Angina requiring treatment	2·98 (1·43–6·24)	0·005
Serum creatinine >0·12 mmol/l	4·27 (1·84–9·89)	0·002
History of dyspnoea	1·96 (0·97–3·97)	0·060
Electrocardiography		
Ischaemic ST segment	2·08 (1·02–4·22)	0·045
Q waves	2·28 (1·13–4·63)	0·022

Values in parentheses are 95 per cent confidence intervals

Table 6 *Independent risk factors for myocardial infarction following aortic surgery*

Factor	Adjusted risk	Risk weighting score
History of transient ischaemic attacks	5·08 (2·01–12·8)	16
Serum creatinine >0·12 mmol/l	3·66 (1·51–8·86)	13
Age >60 years	3·00 (1·00–9·06)	11
Angina requiring treatment	2·74 (1·26–5·92)	10

Values in parentheses are 95 per cent confidence intervals

Table 7 *Cardiac risk prediction score*

Risk score	No. at risk	Sensitivity (%)	Specificity (%)
≥11	418	94	26
≥12	150	69	76
≥17	130	63	79

discriminant analysis. Factors that had significant independent correlation with a postoperative cardiac event were weighted to construct a single discriminant function. Nine factors were given points according to the weighting. A history of myocardial infarction within 6 months, jugular venous distension, dysrhythmia and premature ventricular contractions all scored highly; age >70 years, aortic valve disease, biochemical abnormalities and emergency operation all counted less. Patients were classified, according to the sum of the points for all nine factors into four classes: 1, 0–5 points; 2, 6–12 points; 3, 13–25 points; and 4, ≥26 points.

The numbers of the present patients who fell into each of Goldman's four classes and the incidence of myocardial infarction in each class are shown in *Table 4*. There was no statistically significant difference in the incidence of infarction between these groups. Multiple logistic regression analysis was used to examine risk factors that were related to the incidence of myocardial infarction following surgery (*Table 5*). Relative risks, which are measures of the raised risk in one group compared with another, are preserved. For example, a patient with a history of transient ischaemic attacks has a 3·87 times greater chance of a postoperative myocardial infarction than one without such a history. After adjusting for the interrelationships between all the risk factors, four independent risks were identified. These were, in decreasing order of significance, a history of transient ischaemia attacks, serum creatinine concentration >0·12 mmol/l, age >60 years and a history of symptomatic angina requiring regular treatment (*Table 6*).

A clinical scoring system involving these four factors was then constructed to define a cardiac risk score. This score can be used to predict the chances of postoperative myocardial infarction. To evaluate the cardiac risk score in an individual patient, the appropriate weights relating to the four independent risk factors are added. The weights correspond to the degree of risk associated with the factors. The higher the score the higher the risk of postoperative myocardial infarction. A cardiac risk score was calculated for all the patients in the study, and the specificity and sensitivity with regard to the accuracy of prediction of postoperative infarction evaluated for different levels of the score (*Table 7*). Using a score of ≥12 to classify patients as having a high risk of infarction, 69 per cent of postoperative infarcts and 83 per cent of deaths would be predicted and 76 per cent of risk-free patients correctly identified. Of the 35 patients with postoperative infarction, 24 (69 per cent) would have been identified as at high risk using this cardiac risk score and eight (67 per cent) of those who had fatal infarcts would have been identified. In contrast, only 18 (51 per cent) of the 35 patients were classified as having a Goldman index ≥2, with seven (58 per cent) of those who had fatal infarcts being identified.

Discussion

The increased risk associated with symptoms of cerebrovascular disease and renal impairment is almost certainly an expression of widespread arteriosclerosis. Had this method of assessing risk been applied to the present patients, 150 would have been identified as being at risk and meriting sophisticated cardiac investigation. All 95 of the patients identified as at risk on clinical grounds fell into this category.

A policy of selective investigation has considerable cost implications. Every patient need not be investigated by dipyridamole–thallium scanning or multiple-uptake gated acquisition scanning[17]. If patients at low risk can be reliably identified using a scoring system, a stepwise process of selection of patients for operation should be safe. Present results also suggest that it may be unnecessary to admit all patients to an intensive care unit after routine aortic surgery.

References

1. Brown OU, Hollier LH, Pairolero PC *et al.* Abdominal aortic aneurysms and coronary artery disease. *Arch Surg* 1981; **116**: 1484–8.
2. Goldman L. Cardiac risks and complications of non-cardiac surgery. *Ann Intern Med* 1983; **98**: 504–13.
3. Hollier LH, Plate G, O'Brien PC *et al.* Late survival after abdominal aortic aneurysm repair: influence of coronary artery disease. *J Vasc Surg* 1984; **1**: 290–9.
4. Crawford DS, Bomberger RA, Glaser DH, Saleh SA, Russell WL. Aortoiliac occlusive disease factors influencing survival and function following reconstructive operation over a 25 year period. *Surgery* 1981; **90**: 1055–67.
5. Chadwick L, Galland RB. Preoperative clinical evaluation as a predictor of cardiac complications after infrarenal aortic reconstruction. *Br J Surg* 1991; **78**: 875–7.
6. Hertzer NR, Young GR, Kraemer JR *et al.* Coronary artery disease in peripheral vascular patients. A classification of 100 coronary angiograms and results of surgical management. *Ann Surg* 1984; **199**: 223–33.
7. Hertzer HR, Young GR, Bevan EG *et al.* Late results of coronary artery bypass in patients with infrarenal aortic aneurysms. *Ann Surg* 1986; **205**: 360–7.
8. Acinaoure AJ, Rose DM, Kramer MD, Jacobowitz IJ, Cunningham JR. Role of coronary angiography and coronary

artery bypass surgery prior to abdominal aortic aneurysmectomy. *J Cardiovasc Surg* (*Torino*) 1987; **28**: 552–7.

9. Nicolaides AN. The diagnosis and assessment of coronary artery disease in vascular patients. *J Vasc Surg* 1985; **2**: 501–3.
10. Zellner JL, Elliot BM, Robison JG, Hendrix GH, Spicer KM. Preoperative evaluation of cardiac risk using dobutamine–thallium imaging in vascular surgery. *Ann Vasc Surg* 1990; **4**: 238–43.
11. Yeager RA, Weigel RM, Murphy ES *et al.* Application of clinically valid cardiac risk factors to aortic aneurysm surgery. *Arch Surg* 1986; **121**: 278–81.
12. Perry MO, Calcagno D. Abdominal aortic aneurysm surgery: the basic evaluation of cardiac risk. *Ann Surg* 1988; **6**: 738–42.
13. McEnroe CS, O'Donnell TF Jr, Yeager A, Konstam M, Mackey WC. Comparison of ejection fraction and Goldman risk factor analysis to dipyridamole–thallium studies in the evaluation of cardiac morbidity after aortic aneurysm surgery. *J Vasc Surg* 1990; **11**: 497–504.
14. Pasternack PF, Imperato AM, Bear G *et al.* The value of radionucleide angiography as a predictor of perioperative myocardial infarction in patients undergoing abdominal aortic aneurysm resection. *J Vasc Surg* 1984; **1**: 320–5.
15. Goldman L, Caldera DC, Nussbaum SR *et al.* Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977; **207**: 845–9.
16. Jeffrey CF, Kunsman J, Cullen DJ, Brewster DC. A prospective evaluation of cardiac risk index. *Anaesthetist* 1983; **58**: 462–4.
17. Kazmers A, Cerqueira MD, Zieler RE. Perioperative and late outcome in patients with left ventricular ejection fraction of 35% or less who require major vascular surgery. *J Vasc Surg* 1988; **8**: 307–15.

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Autotransfusion in aortic surgery: the Haemocell System 350 cell saver

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Autotransfusion was performed during elective abdominal aortic reconstruction in ten patients using the recently developed Haemocell System 350. A mean of 60 per cent of total blood loss was salvaged, and during operation each patient was autotransfused 1 unit. Good preservation of cellular components, including platelets, was seen after processing with the device, which uses a vortex mixing filter for cell separation. There was no evidence of coagulopathy; mean free plasma haemoglobin levels were slightly raised (17 mg/dl) and plasma heparin concentration was negligible (0·10 units/ml) 4 h after surgery. A transient drop in plasma fibrinogen levels and the appearance of fibrin degradation products in low concentrations (mean 1·5 mg/l) were seen. Oxyhaemoglobin dissociation curves showed the salvaged red blood cells to have a normal affinity for oxygen. Renal and hepatic function remained unaltered and there were no complications attributable to autotransfusion. The device was easy to handle and a trained operator was not required.

The concept of autotransfusion is more than 100 years old[1] but has become the focus of renewed interest over the past two decades[2,3]. Reasons for this are increased requirements of blood during complex operations in elderly patients and the shortage and high cost of homologous blood[4]. Increased awareness of the risk of transmission of the human immunodeficiency virus and hepatitis through use of homologous blood has further encouraged the development of autotransfusion[5,6].

Simple autotransfusion involving the collection and reinfusion of blood without washing the red cells has been studied during major vascular surgery since 1985 and has been found to be safe for the slow collection and reinfusion of up to 1500–2000 ml blood[7–9]. Cell-saving devices that collect and wash red cells by centrifugation then concentrate and resuspend them in saline for transfusion have been in use for many years[10–12]. Although capable of salvaging larger volumes, they have the disadvantages of traumatizing and activating blood components as well as requiring a longer time and a trained operator for blood processing.

The present study investigated the use of a new cell-saving device, which uses a membrane filtration method to separate salvaged blood, in patients undergoing aortic surgery. Because of its simpler and gentler cell separation the device aims to limit red cell damage, reduce processing time and eliminate the need for a trained operator.

Patients and methods

Between June and August 1991, the Haemocell System 350 (Haemocell, Abingdon, UK) was used to salvage intraoperative blood lost in ten patients undergoing elective abdominal aortic surgery. There were six men and four women, of mean age 65·9 (range 44–78) years. Five patients were operated on for aortic aneurysm and five for aortoiliac occlusive disease. Investigation before operation showed that all patients had normal haematological and coagulation profiles and renal and hepatic function. No patient was using aspirin or anticoagulant therapy before surgery.

All operations were performed under general anaesthesia and routine haemodynamic monitoring. Heparin (150 units/kg) was given intravenously before blood collection. First, 20 ml heparinized saline (5000 units/dl) was sucked in to moisten the filter in the reservoir. Pooled and free-flowing blood was then sucked from the abdominal cavity into plastic reservoirs using a low-pressure (80–100 mmHg) vacuum source. In seven of the ten patients the effect of heparin was reversed with 50–100 mg protamine after blood salvage was complete.

Cell separation was performed by passing the collected blood through a vortex mixing filter with longitudinal channels approximately 60 × 0·75 mm in section and bounded by membrane. The concentrated cellular components were then pumped into a cell-washing reservoir where they were mixed with saline before being passed through the filter for a second time. Finally, the cells and remaining liquid were pumped into a reinfusion reservoir; this concentrated red cell suspension was immediately reinfused into the patient through a 40-μm filter. The overall timescale is shown in *Figure 1*.

Each patient received 1 unit salvaged blood during operation; this was the only blood transfused during surgery in five patients. Two patients received 3 units each, two patients 2 units each and one patient 1 unit homologous blood during operation. In addition, after operation four patients received 2 units and three patients 1 unit homologous blood. In two of the ten patients the 1 unit autologous blood was the only blood transfused throughout the hospital stay. Two patients underwent re-exploration for intra-abdominal bleeding 3 and 5 h after initial surgery. During the second exploration, the first patient received 2 units fresh frozen plasma and the second 4 units fresh frozen plasma plus 6 units platelets. In both patients a source of bleeding was identified (back-bleeding from the inferior mesenteric artery in one and median sacral artery in the other), and no evidence of coagulopathy was found. Both patients had normal coagulation profiles 4 h after initial surgery. There were no deaths.

Venous blood was collected before surgery and at 4 and 24 h after operation. Samples of blood were also taken from the collection reservoir before filtration (R1) and from the reinfusion reservoir before the blood was returned to the patient (R2). Haemoglobin, haematocrit, white cell count (WCC), platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), and levels of fibrinogen and fibrin degradation products were estimated in each blood sample. Fibrin degradation products were estimated by the D-dimer screening test using antifragment D antibody-based latex agglutination. The extent of haemolysis was assessed by spectrophotometric estimation[13] of free plasma haemoglobin. Plasma heparin was assayed by an

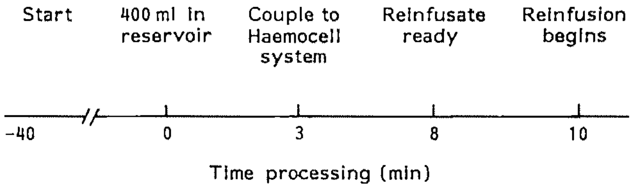

Figure 1 *Timescale of autotransfusion of blood using the Haemocell System 350*

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automated method using a chromogenic substrate to measure anti-Xa activity[14].

Oxyhaemoglobin dissociation curves of paired samples of processed and venous blood drawn from each patient contemporaneously with the collection of blood from the operative field were plotted using an automated tonometer (Hemox-Analyser Model B; TCS Medical Products, Philadelphia, Pennsylvania, USA). These curves were plotted at pH 7·4 and 37°C and the partial pressures of oxygen required to produce 50 per cent haemoglobin saturation (P_{50}) compared[15].

Postoperative biochemical analyses included determination of blood urea and serum creatinine levels to assess renal function, and estimation of total protein, bilirubin and serum calcium concentrations.

Statistical analysis was carried out using Student's paired *t* test and repeated measures of analysis of variance as appropriate.

Results

The mean intraoperative blood loss was 730 (range 500–1200) ml and mean volume salvaged 435 ml (59·6 per cent of total loss, range 41·6–72·0 per cent).

The mean haemoglobin level decreased from a preoperative value of 13·4 g/dl to 12·8 g/dl at 4 h and 12·7 g/dl at 24 h after surgery; mean haematocrit values showed a similar pattern (*Figure 2*). These reductions in haemoglobin level and haematocrit were not statistically significant. There was a significant rise ($P = 0·004$) in mean WCC from a preoperative value of 8·25 × 10^9/l to 13·9 × 10^9/l at 4 h and 12·4 × 10^9/l at 24 h after operation. The platelet count declined from a mean preoperative level of 279 × 10^9/l to 219 × 10^9/l at 4 h and 183 × 10^9/l at 24 h. Although this drop was statistically significant ($P = 0·001$), the count fell below 150 × 10^9/l in only two patients, and did not result in any bleeding complications after operation.

Slight increases in haemoglobin level, haematocrit, WCC and platelet count from sample R1 to R2 were consistent with filtration and concentration of cellular components in the salvaged blood (*Figure 2*). Mean(s.e.m.) free plasma haemoglobin levels were 412(89) mg/dl in R1, falling to 276(45) mg/dl after processing. The mean(s.e.m.) systemic levels were 17(9) mg/dl at 4 h and 8(3) mg/dl at 24 h after surgery.

Figure 3 shows serial changes in coagulation parameters. The PT ratio increased significantly ($P = 0·011$) from a preoperative mean(s.e.m.) of 1·01(0·01) to 1·09(0·03) at 4 h and 1·16(0·04) at 24 h. APTT ratios showed no significant change. The mean(s.e.m.) preoperative plasma fibrinogen level of 3·81(0·45) g/l dropped significantly ($P = 0·001$) at 4 h to 3·09(0·59) g/l and recovered to 3·95(0·40) g/l at 24 h after operation. Sample R2 contained little fibrinogen because of losses during processing. The median level of fibrinogen degradation products was 3·8 mg/l in R1 and fell significantly ($P < 0·04$) to 2·8 mg/l in R2. Systemic levels remained steady at 1·5 mg/l at 4 and 24 h after operation. The mean(s.e.m.) heparin concentration in R1 was 5·76(1·11) units/ml, falling to 4·93(0·91) units/ml in R2. Heparin was virtually absent from the systemic circulation at 4 and 24 h (0·10 and 0·00 units/ml respectively).

The oxygen-carrying capacity of the salvaged red blood cells remained normal from comparison of oxyhaemoglobin dissociation curves. The mean(s.e.m.) fractional difference between the P_{50} of venous blood and R2 was not statistically significant (−2·81(3·05) per cent).

The results of biochemical analyses are shown in *Table 1*. Renal function remained normal after operation. A significant rise ($P = 0·027$) in mean bilirubin level at 24 h was noted, although it remained within the normal range. Mean circulating

Table 1 *Biochemical analysis of blood before and after autotransfusion*

	Before operation	4 h after operation	24 h after operation
Total protein (g/l)	70·5(1·8)	53·3(1·4)*	53·3(1·3)*
Bilirubin (mmol/l)	7·0(0·9)	9·9(2·3)	13·5(1·9)†
Urea (mmol/l)	5·9(0·5)	5·6(0·4)	6·4(0·7)
Creatinine (mmol/l)	0·11(0·01)	0·11(0·01)	0·12(0·01)
Calcium (mmol/l)	2·37(0·04)	2·00(0·04)*	1·99(0·06)*

Values are mean(s.e.m.). $^*P = 0·001$; $^†P = 0·027$ (*versus* preoperative value, Student's *t* test)

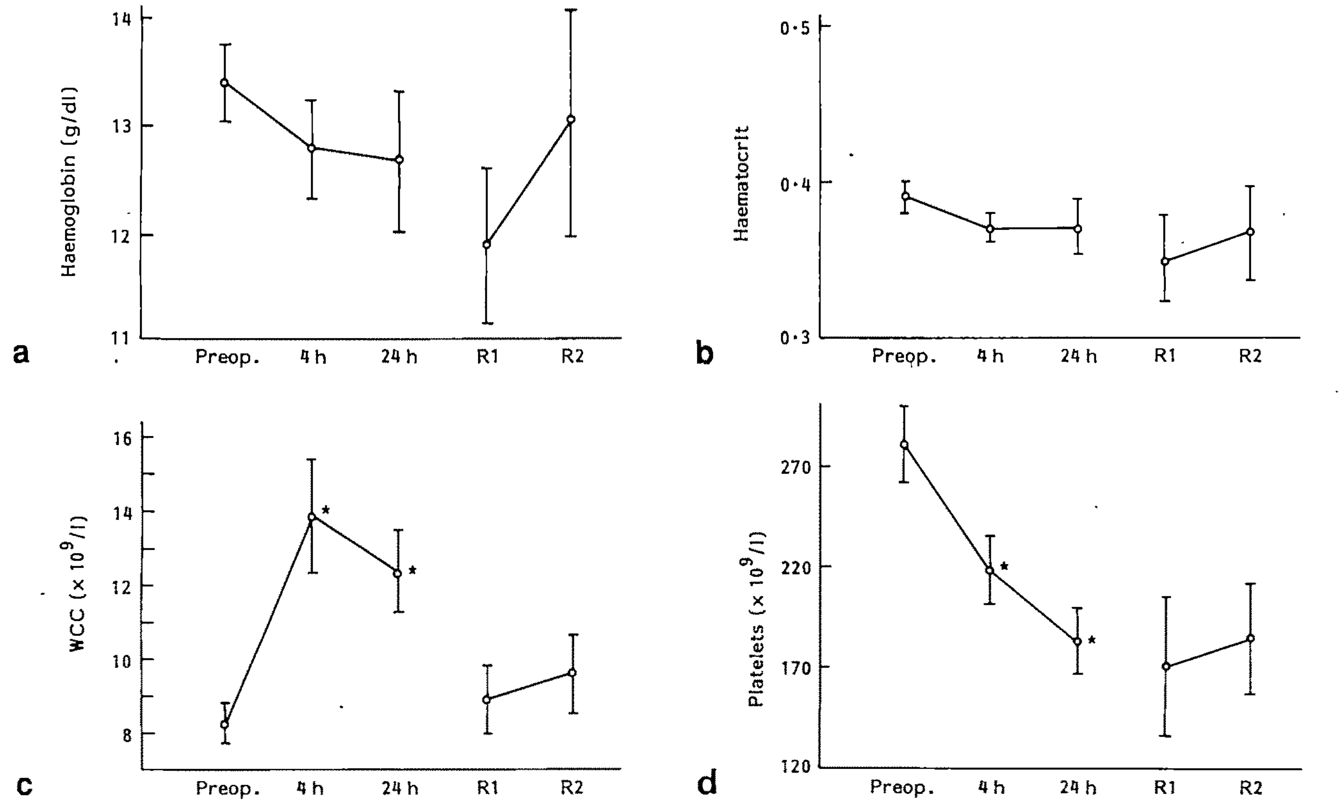

Figure 2 *Changes in* **a** *haemoglobin level,* **b** *haematocrit,* **c** *white cell count (WCC) and* **d** *platelet count. Values are mean(s.e.m.). Salvaged blood: R1, from reservoir before filtration; R2, from reservoir before return to patient.* $^*P < 0·005$ versus *preoperative value (analysis of variance)*

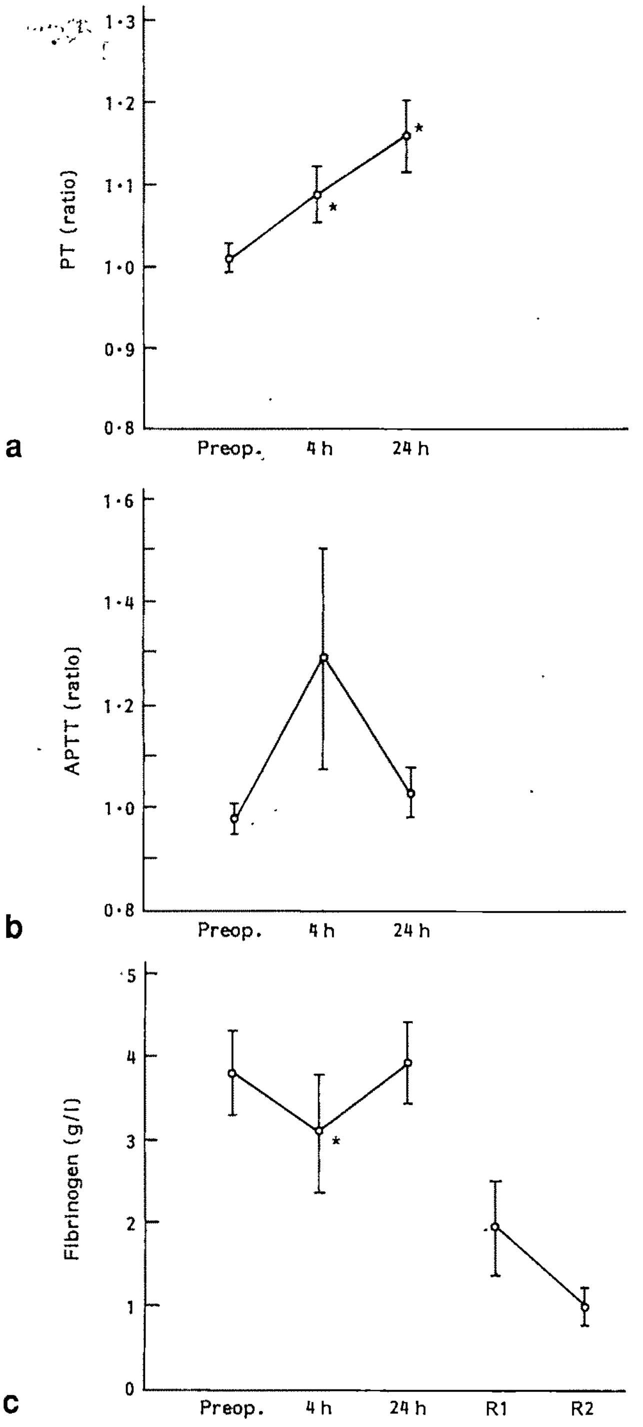

Figure 3 *Changes in* **a** *prothrombin time (PT),* **b** *activated partial thromboplastin time (APTT) and* **c** *plasma fibrinogen level. Values are mean(s.e.m.). Salvaged blood: R1, from reservoir before filtration; R2, from reservoir before return to patient.* *P < 0·005 versus *preoperative value (analysis of variance)*

serum protein levels dropped significantly ($P = 0{\cdot}001$), liver enzyme levels remained within the normal range and serum calcium levels dropped significantly ($P = 0{\cdot}001$) after surgery.

Discussion

Intraoperative autotransfusion has become widely accepted over the past decade; routine and emergency aortic surgery are accepted indications for its use[11,16]. The commonly used cell-saving devices wash and centrifuge red cells before suspending them in saline. Although a large volume of blood salvaged in this way has been safely transfused[11,12], these devices can traumatize and activate blood components, resulting in haemolysis-related renal and hepatic dysfunction and coagulopathies[17,18]. Additional adverse effects include air embolism, microembolism, platelet and fibrinogen loss, and changes in 2,3-diphosphoglycerate affecting oxygen-carrying capacity of red blood cells[10,19].

In recent years, simple autotransfusion devices, via which collected blood is immediately transfused without washing the red cells, have reduced both complexity and cost of the procedure[9]. However, these devices have been shown to be safe from coagulopathy and haemolysis only below volumes of salvage and reinfusion of 2000 ml, with the anticoagulant dose and presence of other contaminants being limiting factors[7,8]. These systems, designed for use during slow intraoperative blood loss, are not helpful in severe rapid haemorrhage[20]. Survival of red cells autotransfused using such systems is similar to that of non-salvaged cells[21].

The Haemocell System 350 employed in the present study uses filtration aided by the fluid dynamic technique of vortex mixing, which allows highly efficient separation of liquid and cellular components of blood[22]. Vortex mixing is a process in which blood is agitated in a defined reproducible way as it crosses a microporous plastic membrane, allowing only soluble components to pass through. It reduces the tendency of cells to bind to the membrane surface, allowing filtration to continue assisted by a low pressure differential (<100 mmHg) across the membrane. Wetting the membrane with saline before processing reduces the frictional forces experienced by the cellular components and eliminates virtually all cell damage. The device is simple to use and does not require a trained operator. A full wash requires 10 min to process 500 ml blood. The concentration step alone can be performed in 5 min in an emergency.

In the present study each patient was transfused with only 1 unit salvaged blood; there were no complications attributable to salvage and reinfusion. In both patients re-explored for bleeding, a source of haemorrhage was identified; no evidence of coagulopathy was found.

Good preservation of cellular components including platelets was seen. Although there was an overall drop in platelet count, it remained within normal limits. Additional bank blood transfused may have been responsible because the two patients who received no bank blood showed an insignificant fall in platelet count. The level of plasma haemoglobin, present in significant amounts in salvaged blood, was reduced during processing; concentrations in peripheral blood were just above normal at 4 h and normal at 24 h after surgery. Heparin was effectively removed during filtration; the levels in systemic blood were extremely low 4 h after operation. A transient fall in fibrinogen concentration was seen but this returned to normal within 24 h. This finding is consistent with a previous study, which showed that the plasma fibrinogen level falls during and after aortic surgery but is not mirrored by increases in fibrin breakdown products[23]. Small amounts of fibrin degradation products were detected in the systemic circulation at 4 and 24 h after operation; significant quantities were removed during processing of salvaged blood. Renal and hepatic function remained normal after surgery.

The functional capacity of red blood cells prepared for reinfusion by the cell saver was found to be unaltered. Stored blood may have a leftward shift of the oxyhaemoglobin dissociation curve because of depleted intracellular 2,3-diphosphoglycerate[19,24]. This may impair oxygen delivery to the tissues and cause cellular hypoxia. The blood from the cell saver had normal oxygen affinity and was physiologically suited to oxygen delivery. It may thus be advantageous to use autotransfusion for patients with potentially impaired oxygen delivery, e.g. the elderly, during pregnancy and in patients with ischaemic vascular disease, renal failure or anaemia.

This study establishes the clinical and haematological safety of the Haemocell 350 System. Further work involving salvage and reinfusion of larger volumes of blood is required to assess the functional capacity of this new cell saver. Its ease of operation and cost-effectiveness make it suitable for widespread use even in small peripheral centres.

References

1. Highmore W. Practical remarks on an overlooked source of blood supply for transfusion in postpartum haemorrhage. *Lancet* 1874; **i**: 89.
2. Klebanoff G. Early clinical experience with a disposable unit for the intraoperative salvage and reinfusion of blood loss (intraoperative autotransfusion). *Am J Surg* 1970; **120**: 718–22.
3. Brener BJ, Raines JK, Darling RC. Intraoperative autotransfusion in abdominal aortic resections. *Arch Surg* 1973; **107**: 78–84.
4. Cutler BS. Avoidance of homologous transfusion in aortic operations: the role of autotransfusion, hemodilution, and surgical technique. *Surgery* 1984; **95**: 717–22.
5. Editorial. Transfusion associated AIDS – a cause for concern. *N Engl J Med* 1984; **310**: 115–16.
6. Popovsky MA, Devine PA, Taswell HF. Intraoperative autologous transfusion. *Mayo Clin Proc* 1985; **60**: 125–34.
7. Maloney RD, Valeri CR. Autotransfusion during vascular surgery with a new simple disposable system. *Proceedings of the New England Society for Vascular Surgery Twelfth Annual Meeting*. Boston, Massachusetts, 1985.
8. Clifford PC, Kruger AR, Smith A, Chant ADB, Webster JHH. Salvage autotransfusion in aortic surgery: initial studies using a disposable reservoir. *Br J Surg* 1987; **74**: 755–7.
9. Duchateau J, Nevelsteen A, Suy R *et al.* Autotransfusion during aorto-iliac surgery. *Eur J Vasc Surg* 1990; **4**: 349–54.
10. O'Hara PJ, Hertzer NR, Santilli PH, Beven EG. Intraoperative autotransfusion during abdominal aortic reconstruction. *Am J Surg* 1983; **145**: 215–20.
11. Hallet JW Jr, Popovsky M, Ilstrup D. Minimising blood transfusions during abdominal aortic surgery: recent advances in rapid autotransfusion. *J Vasc Surg* 1987; **5**: 601–6.
12. Warnock DF, Davison JK, Brewster DC, Darling RC, Abbott WM. Modification of the Haemonetics Cell Saver for optional high flow rate autotransfusion. *Am J Surg* 1982; **143**: 765–8.
13. Fleming AF. A spectrophotometric method for the quantitative estimation of bilirubin in liquor amnii. *Clin Chim Acta* 1965; **12**: 67–74.
14. Cate HT, Lamping RJ, Henny CP, Prins A, Cate JT. Automated amidolytic method for determining heparin, a heparinoid, and low-M_R heparin fragment, based on their anti-FXa activity. *Clin Chem* 1984; **30**: 860–4.
15. Beech MJ, Pollard BJ. Effect of IV anaesthetic agents on the affinity of haemoglobin for oxygen. *Br J Anaesth* 1988; **61**: 497–8.
16. Brewster DC, Ambrosino JJ, Darling RC *et al.* Intraoperative autotransfusion in major vascular surgery. *Am J Surg* 1979; **137**: 507–13.
17. Rakower SR, Worth MH Jr, Lackner H. Massive intraoperative autotransfusion of blood. *Surg Gynecol Obstet* 1973; **137**: 633–6.
18. Duncan SE, Edwards WH, Dale WA. Caution regarding autotransfusion. *Surgery* 1974; **76**: 1024–30.
19. Lambertsen CJ. Transport of oxygen and carbon dioxide by the blood. In: Mountcastle VB, ed. *Medical Physiology*. St Louis, Missouri: Mosby, 1974: 1399–422.
20. Editorial. Blood conservation. *Br J Anaesth* 1991; **66**: 281–4.
21. Kent P, Ashley S, Thorley PJ, Shaw A, Parkin A, Kester RC. 24-Hour survival of autotransfused red cells in elective aortic surgery: a comparison of two intraoperative autotransfusion systems. *Br J Surg* 1991; **78**: 1473–5.
22. Bellhouse BJ, Lewis RWH. A high efficiency membrane separator for donor plasmapheresis. *Transactions of the American Society for Artificial Internal Organs* 1988; **34**: 747–54.
23. Mashiah A, Thomson JM, Poller L, Charlesworth D. Changes in the coagulation of blood during resection of the abdominal aorta. *Surg Gynecol Obstet* 1979; **149**: 214–16.
24. Macdonald R. Oxygen delivery by haemoglobin. In: Scurr C, Feldman S, eds. *Anaesthesia*. 3rd ed. London: William Heinemann, 1977: 406–13.

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Ankle fracture is associated with prolonged venous dysfunction

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Leg swelling is a significant problem following ankle fracture. Venous pump function and femoral and popliteal venous patency were assessed prospectively in 26 patients with ankle fractures requiring open reduction, internal fixation and immobilization in plaster. Functional venous volume, venous filling index (VFI), ejection volume fraction (EVF) and residual volume fraction (RVF) were measured using air plethysmography at 5 days and at 6, 12 and 18 weeks after fracture. The uninjured leg was used as a control. Popliteal and femoral venous patency was determined using duplex ultrasonography. No patient developed deep vein thrombosis during the study. At 5 days after fracture there was a significant reduction in mean(s.d.) EVF, 18·2(12·1) versus *55·9(19·5) per cent, and increase in RVF, 87·0(14·3)* versus *42·5(22·2) per cent (both* $P < 0·001$*). Analogous values were similar at 6 weeks, EVF 28·5(21·2)* versus *55·6(21·9) per cent, RVF 82·2(16·8)* versus *48·5(23·8) per cent (both* $P < 0·001$*), and at 12 weeks, EVF 39·1(16·0)* versus *60·3(14·9) per cent, RVF 64·7(18·8)* versus *38·8(13·2) per cent (both* $P < 0·001$*). However, by 18 weeks there was no significant difference in venous function between fractured and control limbs. It is concluded that there is a significant and prolonged impairment in venous pump function following ankle fracture.*

Leg swelling is a significant problem following ankle fracture. Such fractures are usually produced by indirect or torsional forces applied across the ankle and thus are not typically associated with direct venous or lymphatic injury. To attribute swelling simply to the trauma of fracture fails to take account of the persistence of swelling for several months after the original injury. Persistent leg swelling may result from local venous hypertension due either to venous occlusion by thrombosis or reduced venous pumping[1]. Deep vein thrombosis (DVT) following tibial fracture occurs in 16–54 per cent of cases[2,3]. However, no previous reports have described venous function after lower-limb fracture. This study therefore set out to assess venous patency and venous pump function after ankle fracture.

Patients and methods

Between March and December 1990, 59 patients presented with unilateral ankle fracture. Of these, 26 (44 per cent) required open reduction and internal fixation of the fracture followed by immobilization in a plaster cast. Patients with chronic venous disease or a history of DVT were excluded. All 26 patients participated in the study.

Immediately after surgery patients were encouraged to move the ankle joint and a plaster cast was applied on the fifth day after operation. The patients remained non-weight bearing in the cast for 6 weeks. The cast was then removed and active mobilization and partial weight bearing commenced; patients were fully weight bearing by 12 weeks. Duplex ultrasonography and air plethysmography were performed on both legs (fractured and uninjured control) at 5 days after fracture, before the application of the cast. Patients were examined clinically and radiologically, and the venous studies repeated after removal of the cast at 6 weeks and subsequently at 12 and 18 weeks after fracture.

Duplex scanning (Acuson, Mountain View, California, USA) was used to visualize the femoral and popliteal veins and assess the outflow vessels for venous thrombosis[1,4]. An air plethysmograph (APG-1000; ACI Medical, Sun Valley, California, USA) was used to assess the efficiency of lower-limb venous pump function[5–7]. Using this device, several parameters may be measured: (1) the functional venous volume, which is the difference in leg volume between the elevated and dependent positions; (2) the time taken to reach 90 per cent of this volume; the fraction of 90 per cent of venous volume over this time is the venous filling index (VFI), an indication of valvular function; (3) the volume of blood ejected from the leg by a single muscle contraction ('tiptoe manoeuvre'), the ejection volume; and (4) the volume remaining after ten muscle contractions, the residual volume. The volume ejected by a single contraction and that remaining after ten contractions are expressed as fractions of the functional venous volume, the ejection volume fraction (EVF) and residual volume fraction (RVF) respectively. Both EVF and RVF are sensitive indicators of venous pump function[1], and the latter has been shown to correlate closely with ambulatory venous pressure measurements[8]. The presence or absence of outflow-tract obstruction is indicated by measuring venous outflow rates. *Figure 1* illustrates a typical recording taken during a sequence of postural changes and exercise.

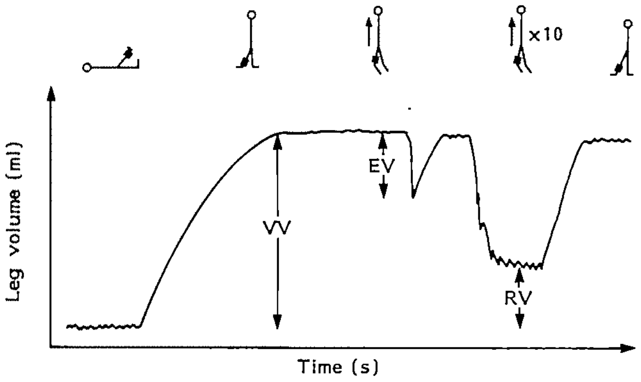

Figure 1 *Typical air plethysmograph tracing with the position of the leg shown schematically. Venous volume (VV), ejection volume (EV) and residual volume (RV) are measured as shown. Venous filling index is calculated by dividing the time taken to reach 90 per cent of VV into this volume. Outflow rate, not shown, is the rate of emptying of the elevated limb following sudden deflation of a venous tourniquet*

All data are expressed as mean(s.d.). Results were compared using Student's *t* test for paired data and the Oxstat computer statistics program (Microsoft, Basingstoke, UK); $P < 0·05$ was regarded as significant.

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Table 1 *Venous function in fractured and non-fractured limbs of 26 patients with unilateral ankle fracture*

	Venous volume (ml)	Venous filling index (ml/s)	Outflow rate (ml/s)	Ejection volume fraction (%)	Residual volume fraction (%)
5 days					
Fracture	114·9(28·5)*	2·3(2·4)	44·5(14·2)	18·2(12·1)*	87·0(14·3)*
Control	78·4(29·8)	1·7(1·8)	44·3(13·2)	55·9(19·5)	42·5(22·2)
6 weeks					
Fracture	90·6(27·0)	1·8(1·4)	45·3(17·8)	28·5(21·2)*	82·2(16·8)*
Control	78·7(23·3)	1·4(1·3)	44·0(12·1)	55·6(21·9)	48·5(23·8)
12 weeks					
Fracture	95·8(32·4)	3·0(2·3)	50·0(14·2)	39·1(16·0)*†	64·7(18·8)*†
Control	95·0(37·4)	1·5(2·4)	46·9(12·8)	60·3(14·9)	38·8(13·2)
18 weeks					
Fracture	96·3(17·7)	3·0(3·2)	50·5(9·2)	57·7(16·3)†	39·9(16·3)†
Control	94·0(28·6)	1·5(1·6)	45·8(11·4)	57·6(17·6)	33·0(16·5)

Values are mean(s.d.). *$P < 0·001$ *versus* control; †$P < 0·001$ *versus* 5 days (Student's *t* test)

Results

Duplex ultrasonography showed no evidence of DVT in the popliteal or femoral veins in any patient either immediately after operation, after removal of the plaster cast at 6 weeks, or at subsequent follow-up at 12 and 18 weeks. Clinical and radiological assessment showed satisfactory progress of healing, with no evidence of demineralization or clinical evidence of reflex sympathetic dystrophy in any patient.

Functional venous volume was significantly greater in the fractured limbs than in controls in the immediate postoperative period. Subsequently, there was no significant difference in venous volume between fractured and control limbs (*Table 1*). VFI and venous outflow in the fractured limbs did not differ significantly from those of the control limbs on any occasion (*Table 1*).

There was a significant reduction in EVF and increase in RVF in fractured limbs compared with controls before application of the cast at 5 days. Both EVF and RVF remained significantly worse in fractured limbs at 6 weeks. At 12 weeks after fracture there was a significant improvement compared with 5-day values in both EVF and RVF. However, both EVF and RVF remained significantly impaired compared with the controls at 12 weeks. By 18 weeks both EVF and RVF in the fractured limbs had returned to normal (*Table 1*).

Discussion

This study has demonstrated for the first time a functional impairment in the venous system following ankle fracture. Furthermore, this abnormality persists for 18 weeks, occurs in the absence of significant obstruction of the femoral or popliteal veins, and is reversible. These findings help elucidate the pathogenesis of leg swelling following fracture. Lower-limb fractures are associated with a high incidence of leg swelling. This is seen primarily in association with tibial fracture, where direct venous injury may lead to a significant incidence of venous thrombosis[2,3] and chronic venous disease[9–11]. The contribution of associated lymphatic injury remains unclear.

Although extensively studied in relation to tibial fracture[2,3], there is a paucity of information on the incidence of venous thrombosis in patients with ankle fractures. Although venography is the 'gold standard' in detecting venous thrombosis in the lower limb, this technique is not without risk. Duplex ultrasonography is an alternative non-invasive test with a sensitivity and specificity of almost 100 per cent for thrombi in the femoropopliteal venous system[12,13] and a sensitivity of 70 per cent for those below knee level[4]. The findings of the present study suggest that significant DVT occurs much less frequently in ankle than tibial fractures (16–54 per cent of cases)[2,3], casting doubt on the need for antithrombotic prophylaxis in the former group of patients. Duplex ultrasonography also showed that significant outflow obstruction was unlikely to be a major contributory factor to swelling in the patients studied.

Venous return from the leg and foot depends primarily on emptying the soleal venous plexus, by contraction of the plantar flexors of the ankle or activation of the plantar venous pump by weight bearing in the presence of an intact valvular system[14]. The finding from air plethysmography that venous volume is significantly greater in limbs with fractures in the immediate postoperative period is not surprising. These results reflect maximal venous pump impairment with consequent dilatation of the capacitance vessels in the soleal plexus. However, at 6 weeks there was no difference in venous volume between fractured and control limbs, and impairment of this particular parameter cannot be advanced as an explanation for limb oedema at this time.

Air plethysmography also demonstrated a significant reversible impairment of calf pump function following ankle fracture. Initially EVF was reduced and RVF increased. At 6 weeks both pain and ankle stiffness are likely to cause impaired pump function. Subsequently, as the patient begins to bear weight on the limb, venous pump function improves. This may reflect increased activity in the plantar venous pump which will function on weight bearing, although ankle joint movement is still restricted. At 12 weeks, although the fracture is healed and the patient fully weight bearing, venous function is still significantly impaired. It is not until 18 weeks that venous pumping returns to normal.

The use of the contralateral uninjured leg as a control does not allow the distinction to be made between the relative contributions of fracture, surgery and subsequent immobilization in plaster to the overall impairment of venous function. Nevertheless, it does demonstrate that the net result of all these factors is to produce a significant impairment of venous pump function. Immobilization in a cast alone is likely to inhibit venous pumping; further studies comparing fractured limbs with and without plaster may help distinguish the effects of fracture and surgery from those of immobilization.

Prolonged limb swelling following ankle and wrist fracture occurs as part of the syndrome of reflex sympathetic dystrophy or algodystrophy. This is characterized by painful swelling associated with erythema, shiny skin and radiological evidence of decreased bone density[15]. The incidence of reflex sympathetic dystrophy following various types of injury and different methods of treatment remains unknown[15]. No patient in this study developed the clinical or radiological features of this syndrome.

This study highlights the prolonged period of recovery after ankle fracture and indicates a need for therapeutic modifications to try to reduce the duration of convalescence. To decrease the morbidity associated with lower-limb swelling following ankle fracture, measures directed towards earlier rehabilitation of the venous pump need to be considered. Where possible serious consideration should be given to managing patients with ankle fracture without a cast, or to using a modified cast such as a hinged below-knee plaster. The use of venous pumps[16] or compression stockings within the cast may be an alternative.

References

1. Nicolaides AN, Sumner DS. Deep vein thrombosis. In: Nicolaides AN, Sumner DS, eds. *Investigation of Patients with Deep Vein Thrombosis and Chronic Venous Insufficiency*. London: Med-Orion, 1991: 5–50.
2. Hjelmstedt A, Bergvall U. Incidence of thrombosis in patients with tibial fractures. *Acta Chirurgica Scandinavica* 1968; **134**: 209–18.
3. Hjelmstedt A, Bergvall U. Phlebographic study of the incidence of thrombosis in the injured and uninjured limb in 55 cases of tibial fracture. *Acta Chirurgica Scandinavica* 1968; **134**: 229–34.
4. Renton S, Crofton M, Nicolaides A. Impact of duplex scanning on vascular surgical practice. *Br J Surg* 1991; **78**: 1203–7.
5. Christopolous DC, Nicolaides AN. Noninvasive diagnosis and quantification of popliteal reflux in the swollen and ulcerated leg. *J Cardiovasc Surg (Torino)* 1988; **19**: 535–9.
6. Christopolous DC, Nicolaides AN, Szendro G. Air plethysmography and the effect of elastic compression on venous haemodynamics of the leg. *J Vasc Surg* 1987; **5**: 148–59.
7. Katz ML, Comerota AJ, Kerr R. Air plethysmography (APG). A new technique to evaluate patients with chronic venous insufficiency. *Journal of Vascular Technology* 1991; **15**: 23–7.
8. Christopolous DC, Nicolaides AN, Cook A, Irvine A, Galloway JMD, Wilkinson A. Pathogenesis of venous ulceration in relation to the calf muscle pump. *Surgery* 1989; **106**: 829–35.
9. Aitken RJ, Mills C, Immelman EJ. The postphlebitic syndrome following shaft fractures of the leg. *J Bone Joint Surg* [*Br*] 1987; **69-B**: 775–8.
10. Lindhagen A, Bergqvist D, Hallbook T, Berndtsson L. Venous function after fracture of the lower extremity; a nine year follow-up of 150 patients. *Acta Orthop Scand* 1985; **56**: 110–14.
11. Willen J, Bergqvist D, Hallbook T. Venous insufficiency as a late complication of tibial fracture. *Acta Orthop Scand* 1982; **53**: 149–53.
12. Hannan LA, Stedje KJ, Skorcz MJ *et al.* Venous imaging of the extremities: our first twenty-five hundred cases. *Bruit* 1986; **10**: 29–32.
13. Semrow CM, Freidell M, Buchbinder D *et al.* Characterisation of lower extremity venous disease using real time B-mode ultrasonic imaging. *Journal of Vascular Technology* 1987; **11**: 187–91.
14. Gardener AMN, Fox RH. The venous pump of the human foot – preliminary report. *Bristol Medicochirurgical Journal* 1983; **98**: 109–12.
15. Van der Griend RA, Savoie FH, Hughes JL. Fractures of the ankle. In: Rockwood CA, Green DP, Bucholz RW, eds. *Rockwood and Green's Fractures in Adults*. Philadelphia: JB Lippincott, 1991: 2000–27.
16. Gardener AMN, Fox RH, Lawrence C *et al.* Reduction of post-traumatic swelling and compartment pressure by impulse compression of the foot. *J Bone Joint Surg* [*Br*] 1991; **72-B**: 810–15.

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Benign parotid cysts associated with human immunodeficiency virus infection

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The development of benign lymphoepithelial parotid cysts in association with human immunodeficiency virus (HIV) infection has recently been reported in the USA, but the condition has yet to be brought to the attention of general surgeons on this side of the Atlantic[1-3]. The diagnosis is an important one, because surgical intervention can be avoided.

Case report

A 32-year-old man known to have been HIV positive since 1986 presented in 1990 with oral candidosis, genital herpes and axillary lymphadenopathy. Clinical examination also revealed bilateral parotid swelling. The man was treated with acyclovir and amphotericin B lozenges and symptoms improved, although both parotid glands continued to enlarge painlessly over the following months. Computed tomography (CT) was performed, revealing multiple cysts within grossly enlarged parotid glands (*Figure 1*) and a 2-cm right submandibular lymph node. The largest cyst was aspirated and found to contain 25 ml dark orange fluid; microscopic examination of this demonstrated lymphocytes and benign epithelial cells. These features were recognized as those of HIV-related benign lymphoepithelial parotid cysts and hyperplastic cervical lymphadenopathy, and parotid surgery was avoided. The parotid swelling has now been present for 2 years, causing no symptoms other than occasional discomfort, which is relieved by outpatient cyst aspiration.

Discussion

Several cases of cystic parotid swelling have now been reported in patients with either acquired immune deficiency syndrome or HIV infection or who are at 'high risk' but of unknown HIV status, and they are usually treated by superficial parotidectomy[1-3]. The features on CT appear to be characteristic, consisting of multiple homogeneous cystic masses with peripheral rim enhancement usually, but not invariably, affecting both glands. Multiple homogeneous cervical lymph nodes up to 2 cm in diameter are frequently seen in association with the condition[4]. The histological features are also characteristic, consisting of cysts lined by cuboidal and squamous epithelium surrounded by lymphoid tissue with prominent germinal centres[1,2,4].

Other causes of cystic parotid disease include retention cysts, congenital first branchial cleft cysts and cystic Warthin's tumours, but these are usually unilateral; congenital polycystic disease of the parotid is rare[4-6]. Malignant swellings of the parotid such as lymphoma or metastatic Kaposi's sarcoma have also been reported in association with HIV infection, but these conditions have quite different clinical and CT appearances[2,3]. The diagnosis of benign lymphoepithelial parotid cysts can thus be confidently made in an 'at-risk' patient on the basis of CT and cytological findings, and indeed this diagnosis may precede other manifestations of HIV-related illness[1,3]. Superficial parotidectomy appears to be unnecessary either for diagnosis or for control of symptoms.

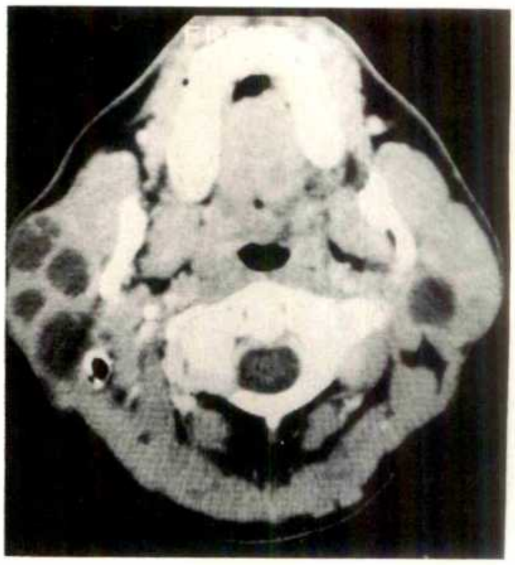

Figure 1 *Computed tomography with intravenous contrast enhancement of the neck, showing bilateral cystic parotid swelling*

References

1. Sperling NM, Lin P-T. Parotid disease associated with human immunodeficiency virus infection. *Ear Nose Throat J* 1990; **69**: 475–7.
2. Finfer MD, Schinella RA, Rothstein SG, Persky MS. Cystic parotid lesions in patients at risk for the acquired immunodeficiency syndrome. *Arch Otolaryngol Head Neck Surg* 1988; **114**: 1290–4.
3. Tunkel DE, Loury MC, Fox CH, Goins MA, Johns ME. Bilateral parotid enlargement in HIV-seropositive patients. *Laryngoscope* 1989; **99**: 590–5.
4. Holliday RA, Cohen WA, Schinella RA *et al.* Benign lymphoepithelial parotid cysts and hyperplastic cervical adenopathy in AIDS-risk patients: a new CT appearance. *Radiology* 1988; **168**: 439–41.
5. Cohen MN, Rao U, Shedd DP. Benign cysts of the parotid gland. *J Surg Oncol* 1984; **27**: 85–8.
6. Seifert G, Thomsen S, Donath K. Bilateral dysgenetic polycystic parotid glands. *Virchows Arch A Pathol Anat Histopathol* 1981; **390**: 273–88.

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Parathyroidectomy in the treatment of patients with chronic renal failure: a 10-year review

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The technique and outcome of surgery for the manifestations of secondary hyperparathyroidism are described. Forty-seven patients were analysed retrospectively over a 10-year period. Total parathyroidectomy and autotransplantation to the forearm was performed in all but five patients. Improvement occurred in 87 per cent of patients and there were no graft failures. Of six deaths, none was related to surgery. Four patients had recurrent hyperparathyroidism, three being graft dependent and one requiring re-exploration of the neck. Total parathyroidectomy and autotransplantation is a safe and effective approach. The major management problem was graft hyperplasia, seen in three of the 47 patients and managed by simple excision.

The physiological response to the prolonged hypocalcaemia of renal failure results in secondary hyperparathyroidism. Early in the disease the effects of excess levels of parathyroid hormone (PTH) can be controlled by medical means. When the mass of functioning parathyroid tissue becomes so great that medical therapy fails, surgical treatment is required. From 3 to 32 per cent of patients on chronic haemodialysis will require surgery for severe hyperparathyroidism[1,2].

Parathyroidectomy has recently become an established treatment for secondary hyperparathyroidism. In 1960, Stanbury *et al.*[3] reported the first patient with complications of secondary hyperparathyroidism undergoing successful elective subtotal parathyroidectomy. In 1967, Ogg[4] introduced total parathyroidectomy, but the procedure lost favour because of the long-term requirement for calcium and vitamin D supplementation. Wells *et al.*[5] in 1975 described the technical success of total parathyroidectomy with autotransplantation of parathyroid fragments into forearm muscle and cryopreservation of reserve parathyroid. This method has proved increasingly popular, with the recent literature reporting minimal problems with graft failure and recurrent hyperparathyroidism[1,2,6-10].

This study analysed the success of surgery in relieving the manifestations of secondary hyperparathyroidism and records experience with total parathyroidectomy and autotransplantation.

Patients and methods

Hospital and private records were analysed retrospectively from 47 patients who had undergone parathyroidectomy for secondary hyperparathyroidism between 1981 and 1991. The accuracy of information retrieved was verified by the current treating nephrologist and the operating surgeon.

There were 20 male and 27 female patients, with a mean age of 45 (range 17-70) years at the time of parathyroidectomy. Thirty-four of the patients were being treated by haemodialysis and three by peritoneal dialysis. One patient required neither and this information was unavailable for another. Eight patients had functioning renal transplants at the time of surgery. Patients were followed for a mean of 40 (range 1-107) months. Forty-six patients underwent surgery for the first time and one required reoperation after previous resection of three and a half glands 10 years earlier.

Preoperative investigations included serial serum calcium, phosphate and alkaline phosphatase estimations. Skeletal surveys were performed at frequent intervals by radiography of the hands, clavicles, thoracolumbar spine and pelvis. Serial PTH levels were also obtained. A variety of PTH assays was used over the 10 years, including *C*-terminal, *N*-terminal and mid-molecule types, but recently the intact molecule has been measured. Bone biopsy from the iliac crest was obtained for histological analysis in the majority of patients. Localization procedures proved of limited value.

Patients were admitted to the renal unit 3 days before surgery. The dose of calcitriol was increased to 500 μg daily on admission. Daily surveillance attempted to maintain serum calcium levels <3 mmol/l and phosphate <2 mmol/l. Dependent patients underwent dialysis on the day before surgery.

The indications for parathyroidectomy are shown in *Table 1*, which gives the most significant severe complication warranting surgical intervention in each patient. No single feature was an absolute indication for surgery and in all cases other confirmatory changes of hyperparathyroidism were present. Active bone disease was established by radiographic and histological demonstration of renal osteodystrophy with progressive bone resorption that had not improved despite appropriate medical therapy. Persistent hypercalcaemia often heralded a failure of medical therapy by precluding the further use of calcitriol. Severe soft tissue calcification unresponsive to tight dietary control of phosphate prompted parathyroidectomy to minimize further ectopic calcification. A severe excess of PTH (at least ten times normal level) with other supporting evidence of hyperparathyroidism was responsible for initiating surgery to prevent calciphylaxis. This fatal syndrome, first described by Selye *et al.*[11], is characterized by progressive ischaemic necrosis of large areas of skin, associated with extensive vascular and soft tissue calcification. Occasionally surgery was indicated for other reasons such as severe bone pain unresponsive to vitamin D administration.

All operations were performed by one of two consultant surgeons using the technique described by Wells *et al.*[5]. Surplus fragments were initially sent for cryopreservation, but this was subsequently discontinued because reimplantation was never necessary.

Total parathyroidectomy and autotransplantation to the forearm was performed in all but five patients. Two patients with calciphylaxis underwent total excision with no autograft, and in three an intraoperative decision was made that subtotal parathyroidectomy would be more appropriate.

Table 1 *Indications for and outcome of parathyroidectomy*

Indication for surgery	No. improved
Active progressive bone resorption	21 of 21 (100)
Persistent hypercalcaemia	8 of 10 (80)
Severe soft tissue calcification	5 of 7 (71)
Parathyroid hormone excess	5 of 6 (83)
Other	2 of 3 (67)
Total	41 of 47 (87)

Values in parentheses are percentages

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Table 2 *Late mortality*

Cause	No.	Time after operation (months)
Calciphylaxis	2	2, 3
Cerebrovascular accident	1	1
Cardiac arrest	1	35
Aortic valve replacement	1	45
Major depression (suicide)	1	84

Table 3 *Morbidity*

Complication	No.
Surgical	
Donor	
Recurrent laryngeal nerve palsy (temporary)	2
Recurrent laryngeal nerve palsy (permanent)	0
Haematoma	4
Infection	2
Graft	
Haematoma	1
Infection	1
General	
Chest infection	6
Pyrexia of unknown origin	2
Fluid overload	1
Hypercalcaemia	1
Tissue necrosis after calcium extravasation	1
Hypertension	1

A technique of intraoperative insertion of a jugular central venous line under direct vision was developed to facilitate management of postoperative hypocalcaemia. After the introduction of this technique in 1986, 13 patients had a central venous line inserted during the operation, with no reported complications.

All patients were closely monitored after operation and calcium levels maintained by slow intravenous infusion of 10 per cent calcium chloride (42 mmol calcium in 500 ml 5 per cent dextrose at 10 ml/h). Serum levels were held between 1·8 and 2·6 mmol/l by adjusting the infusion rate. Calcitriol 1 mg daily and 1 g ionizable calcium tablets three times daily were prescribed as soon as oral intake commenced. Parathyroid status was monitored and the PTH level generally observed to return to normal within 7–10 days. Skeletal radiographic surveys were performed 3, 6 and 12 months after surgery, and bone biopsies were commonly repeated.

Results

In the first 30 days after operation there were no deaths. There were six late postoperative deaths, from 31 days to 7 years afterwards. The causes of these are shown in *Table 2*. Surgery was not a contributing factor and did not influence the course of the two patients with established calciphylaxis.

Table 3 shows the morbidity, with a 21 per cent incidence of complications related to the operation. Surgical drainage was required for one of the haematomas but was not needed for the infected sites. Minor complications of a general nature, such as respiratory tract infection, were observed in 26 per cent of patients.

Improvement, defined by a return to normal in the clinical, laboratory and radiological parameters specific to the particular manifestation of secondary hyperparathyroidism leading to surgery, occurred in 87 per cent of patients (*Table 1*).

There were no cases of permanent hypoparathyroidism and all patients were normocalcaemic without more than 250 μg vitamin D supplementation daily. The maximum duration of intravenous calcium supplementation was 8 (mean 3·7) days. Four patients had recurrent hyperparathyroidism requiring surgery. On three occasions the forearm implants had become hyperplastic and were surgically reduced. In the fourth patient there was no macroscopic parathyroid tissue present at the time of forearm re-exploration, and a supernumerary gland was subsequently resected from the neck. The three patients who developed graft-dependent hypercalcaemia all had rising PTH and calcium levels. In two patients, palpable nodules were present in the forearm; in the third, ultrasonography showed the focal mass of parathyroid tissue in the forearm. In all cases forearm exploration was carried out under local anaesthesia, recurrent hyperplastic glands found and significant graft reductions carried out.

Of the 47 patients, 43 had complete parathyroidectomies confirmed histologically: 41 patients had four glands identified at surgery, one patient had five glands, and one patient had only the solitary remaining gland identified at reoperation, after resection of three and a half glands 10 years earlier. Persistent hyperparathyroidism might have been anticipated in the four patients where histological analysis indicated parathyroidectomy may have been incomplete, but it was observed in only two. A missed accessory gland accounted for a third case of persistent disease.

Discussion

Earlier publications[1,2,8,12] confirm that the duration of the present study, the patient numbers and the mean follow-up compare favourably with those of previous series. Because of the diverse manifestations of hyperparathyroidism, postoperative assessment can be difficult to quantify. By directing attention to the particular manifestation for which the operation was performed, 87 per cent of patients achieved resolution of the main problem and a reduction in hyperparathyroidism generally. Previous studies have discussed indications for surgery and outcome[1,7,8,10,13,14], but not assessed them in this stratified manner.

The low morbidity and mortality rates seen in the present series indicate that the operative strategies chosen were safe. Although the morbidity rate approached 26 per cent, the minor nature of these complications must be taken into account. None of the deaths implicated surgery as a contributing factor, and over a 10-year period no patient was rendered hypoparathyroid. This is in accordance with the results of other large series, which report rates of failure in the range of 5 per cent or less[6].

The most appropriate operation for secondary hyperparathyroidism is still unresolved, despite attempts to compare the efficacy of the two available procedures[15]. In theory, total parathyroidectomy with autograft is better than subtotal parathyroidectomy because recurrence in forearm autografts is more easily controlled (by excision under local anaesthesia) than recurrence in the neck, which requires an operation that is technically difficult and associated with a significant risk of hypoparathyroidism and recurrent laryngeal nerve damage[1,6,9,16]. In previous reports the majority of recurrences have required neck re-exploration for overlooked parathyroid tissue[12,16,17]. This has negated the theoretical advantages of a simple reduction procedure in the forearm and led to subtotal parathyroidectomy being the favoured procedure.

Pronounced postoperative hypocalcaemia is a predictable sequel to parathyroidectomy. The hypocalcaemia is attributable to delayed function of the graft or parathyroid remnant and the 'hungry bones' of severe osteitis fibrosa cystica. Several studies have reported problems with inadequate calcium replacement in this situation[6,12]. The protocol of aggressive postoperative calcium replacement has overcome this problem. With the central venous line inserted at surgery, a calcium infusion commences immediately after operation. This technique eliminates the risk of skin necrosis, which occurs if calcium extravasates from a peripheral intravenous line.

References

1. Rothmund M, Wagner PK. Total parathyroidectomy and autotransplantation of parathyroid tissue for renal hyperparathyroidism. *Ann Surg* 1983; **197**: 7–16.

2. Diaz-Buxo JA, Geissinger WT, Walker JT *et al.* Total parathyroidectomy and autotransplantation. *Clin Nephrol* 1981; **16**: 276–82.
3. Stanbury SW, Lumb GA, Nicholson WF. Elective subtotal parathyroidectomy for renal hyperparathyroidism. *Lancet* 1960; **i**: 793–8.
4. Ogg CS. Total parathyroidectomy in treatment of secondary (renal) hyperparathyroidism. *BMJ* 1967; **iv**: 331–4.
5. Wells SA, Gunnells JC, Shelburne JD, Schneider AB, Sherwood LM. Transplantation of the parathyroid glands in man. Clinical indications and results. *Surgery* 1975; **78**: 34–44.
6. Harding AD, Nichols WK, Mitchell FL. Total parathyroidectomy and autotransplantation in hyperplasia of the parathyroid gland. *Surg Gynecol Obstet* 1990; **171**: 288–90.
7. Lando MJ, Hoover LA, Zuckerbraun L, Goodman D. Autotransplantation of parathyroid tissue into sternocleidomastoid muscle. *Arch Otolaryngol* 1988; **114**: 557–60.
8. Diethelm AG, Adams PL, Murad TM *et al.* Treatment of secondary hyperparathyroidism in patients with chronic renal failure by total parathyroidectomy and parathyroid autograft. *Ann Surg* 1982; **193**: 777–93.
9. Mallette LE, Eisenberg KL, Schwaitzberg SD, Suki WN, Noon GP. Total parathyroidectomy and autogenous parathyroid graft for treatment of hyperparathyroidism due to chronic renal failure. *Am J Surg* 1983; **146**: 727–33.
10. Llach F. Parathyroidectomy in chronic renal failure. *Kidney Int* 1990; **38**(Suppl 29): S62–8.
11. Selye H, Gabbiani G, Strebel R. Sensitization to calciphylaxis by endogenous parathyroid hormone. *Endocrinology* 1962; **71**: 554–8.
12. Levitt MD, Vivian AB, Saker BM. Parathyroidectomy in chronic renal failure. *Aust N Z J Surg* 1986; **56**: 233–9.
13. Welk RA, Alix DR. A community hospital experience with total parathyroidectomy and autotransplantation for renal hyperparathyroidism. *Am Surg* 1987; **53**: 622–7.
14. De Francisco AM, Ellis HA, Owen JP *et al.* Parathyroidectomy in chronic renal failure. *Q J Med* 1985; **55**: 289–315.
15. Nichols P, Owen JP, Ellis HA, Farndon JR, Kelly PJ, Ward MK. Parathyroidectomy in chronic renal failure: a nine-year follow-up study. *Q J Med* 1990; **77**: 1175–93.
16. Rothmund M, Wagner PK. Reoperations for persistent hyperparathyroidism. *Ann Surg* 1988; **207**: 310–14.
17. Siges-Sierra A. Indications and late results of subtotal parathyroidectomy and hyperparathyroidism after renal transplantation. *World J Surg* 1984; **8**: 534–9.

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Timing of surgery for breast cancer in relation to the menstrual cycle and survival of premenopausal women

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Recent studies[1,2] have reported a significant reduction in overall and disease-free survival rates in premenopausal women with operable breast cancer undergoing surgery during the follicular rather than the luteal phase of the menstrual cycle. Others[3–5] have not been able to confirm this relationship. The records of patients seen at the William Harvey Hospital were therefore examined to test this hypothesis.

Patients and methods

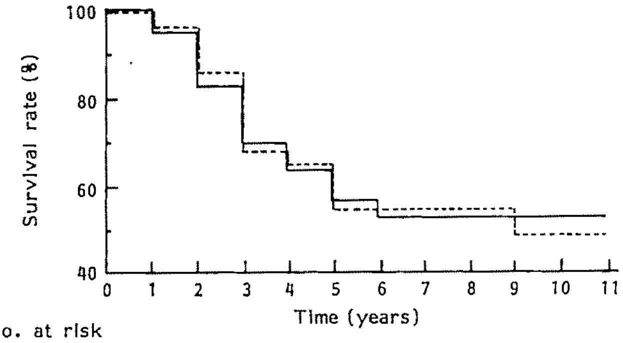
The records of 227 premenopausal women with operable breast cancer treated between 1979 and 1988 were studied. All were followed up at regular intervals. Women with unknown last menstrual period, irregular cycles or who were taking the contraceptive pill were excluded. Complete data were available for 132 patients.

The interval between onset of the last menstrual period and first surgical 'interference' with the tumour (Tru-Cut (Travenol Laboratories, Deerfield, Illinois, USA) or fine-needle biopsy, excision biopsy or mastectomy) was used to divide patients into two groups. A putative time of ovulation was set 13 days after the first day of the last menstrual period. Group 1 patients ($n = 40$) underwent excision or needle biopsy between days 3 and 12 of the cycle and group 2 ($n = 92$) between days 0 and 2 or between days 13 and 33. The data were then reanalysed discounting any needle biopsy, using the date of removal of the tumour by excision or mastectomy to separate the patients into two groups by the same criteria.

Tumour stage, size and type were compared using the χ^2 test. Overall and disease-free survival rates were calculated by the Kaplan–Meier product limit estimate method and compared using the log rank test. Hazard ratios were calculated using Cox's regression model.

Results

Tumour stage, size and type were similar in the two groups. There was no difference between them in overall survival rate (*Figure 1*) or in disease-free survival rate (data not shown). This was true whether the relation to the menstrual cycle was calculated from the first intervention or from the first inpatient surgical procedure. The hazard ratio (group 1:group 2) for overall survival was 0·99 (95 per cent confidence interval 0·56–1·70) and for disease-free survival 0·87 (95 per cent confidence interval 0·52–1·46).



No. at risk	0	2	4	6	8	10
Group 1	40	38	25	15	7	2
Group 2	92	88	58	32	14	4

Figure 1 *Survival rate in relation to timing of first inpatient operation.* —, *Group 1* (*operation between days 3 and 12 of cycle*); -----, *group 2* (*days 0–2 or 13–33*). P = *0·96* (*log rank test*)

Discussion

After studies on mice, in which metastases were found to occur more frequently if resection of a breast tumour was undertaken close to the time of ovulation, a similar relationship between survival and the timing of surgery was observed in a small number of premenopausal women. The hazard was greatest when surgery was performed during the perimenstrual period. Subsequent reports utilizing the same menstrual cycle divisions failed to show any differences.

Both Senie *et al.*[1] and Badwe and colleagues[2] have reported an increased hazard for women whose tumour was excised during the luteal phase and suggested that this might be the effect of unopposed oestrogen. The present results support reports by Powles *et al.*[3], Low and co-workers[4], Goldhirsch and colleagues[5] and others in finding no relation between the timing of surgery and survival. Prospective studies should be carried out with biochemical analyses to determine the phase of the menstrual cycle more accurately before a major change in surgical practice is recommended.

References

1. Senie RT, Rosen PP, Rhodes P, Lesser ML. Timing of breast cancer excision during the menstrual cycle influences duration of disease-free survival. *Ann Intern Med* 1991; **115**: 337–42.
2. Badwe RA, Gregory WM, Chaudary MA *et al.* Timing of surgery during menstrual cycle and survival of premenopausal women with operable breast cancer. *Lancet* 1991; **337**: 1261–4.
3. Powles T, Ashley SE, Nash AG, Tidy A, Gazette J, Ford HT. Timing of surgery in breast cancer. *Lancet* 1991; **337**: 1604 (Letter).
4. Low SC, Galea MH, Blamey RW. Timing breast cancer surgery. *Lancet* 1991; **338**: 691 (Letter).
5. Goldhirsch A, Gelber RD, Forbes J *et al.* Timing breast cancer surgery. *Lancet* 1991; **338**: 692 (Letter).

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Surgical workshop

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Centroinferior hemimastectomy

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An important objective in the surgical treatment of small (<2 cm) breast cancers is the application of conservative surgical techniques. The elliptical radial quadrantectomy[1] satisfies this requirement for the upper breast quadrants, although it is impractical in the centroinferior quadrants. The most common consequence following inferior quadrantectomy is the noticeable deformity and excessive protrusion and down-pointing of the nipple caused by fibrosis and retraction[2,3]. Central cylindrical quadrantectomy requires a difficult breast reconstruction because of resulting local glandular and skin deficit[2,3]. An alternative operative technique for tumours of the centroinferior parts of the breast is reported.

Surgical technique

The technique is similar to that of reduction mammoplasty with a superior pedicle[4].

Marking (*Figure 1a*) occurs before operation. With the patient standing, the inframammary fold and its intersection with the mid-clavicular line at point D are noted. The new position of the nipple (point A) is fixed on the mid-clavicular line 19–21 cm from the jugular notch. An inverted V with its vertex at A, ending at B (medial) and C (lateral) about 7 cm below it and containing the nipple–areola complex, marks out the skin incision. The distance between B and C is determined by drawing them together with minimum tension while holding the breast upwards. Bringing together B, C and D gives an idea of the volume of breast that will remain and ensures ease of reconstruction. The shortest straight line joining B and C with the inframammary fold completes incision mapping.

With the patient supine for the operation, a circular skin incision of 4 cm diameter centred on the nipple is made. Incisions are also made over lines AB and AC. The area between the two incisions is dissected, leaving the nipple attached to the underlying tissues. The area of breast containing the tumour, with at least 2–3 cm of healthy tissue, is excised to the deep fascia, from line BC inferiorly to the inframammary fold (*Figure 1b*). The reconstruction is performed by joining B, C and D with an intradermal stitch (*Figure 1c*), while holding up the de-

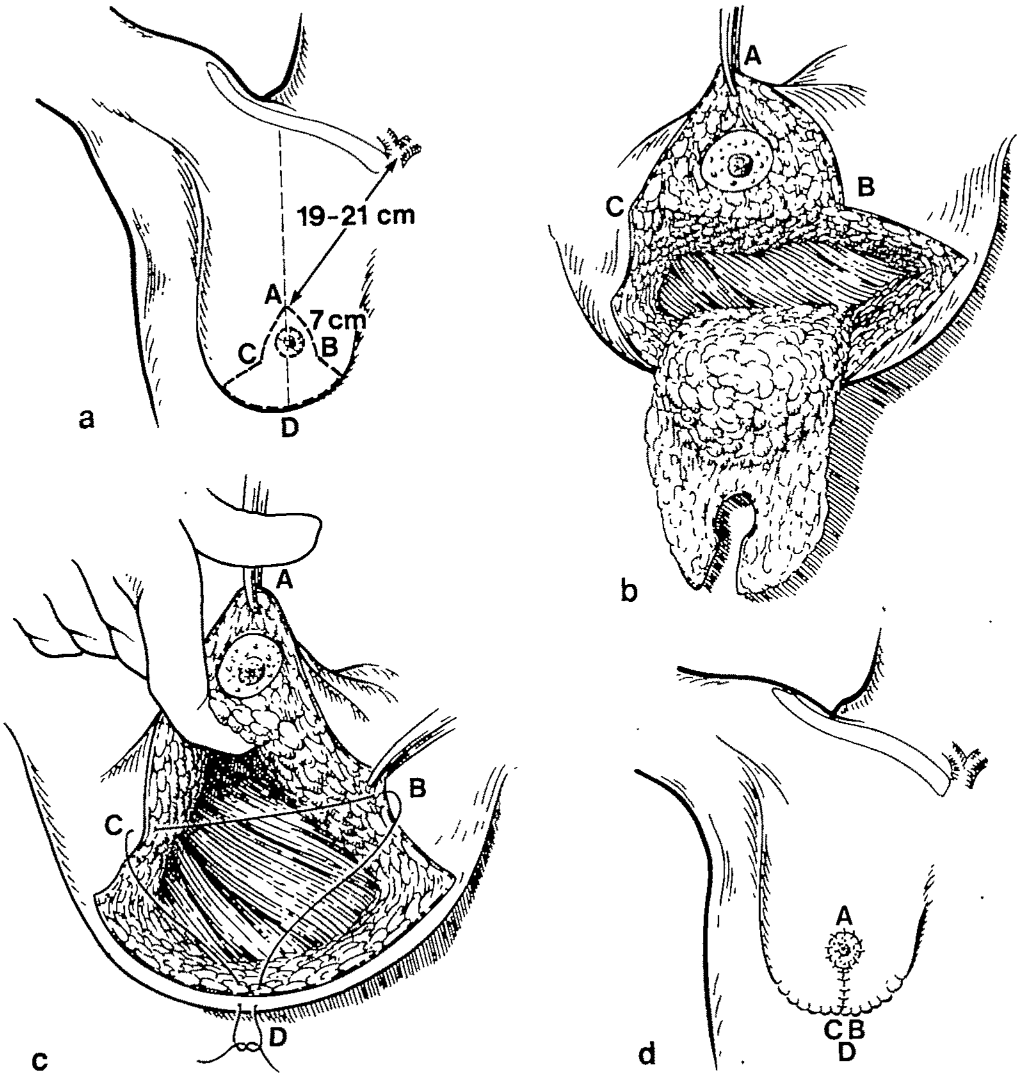

Figure 1 *Incision plan and operative steps of centroinferior hemimastectomy*

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epithelialized triangular portion of the remaining breast. The vertical (AB and AC) and horizontal (inframammary fold) incisions are closed with skin stitches producing an inverted T (*Figure 1d*). The nipple–areola complex is made to emerge through the circular skin incision and sutured separately. For centrally located tumours, the technique allows removal of all breast tissue contained between lines AB and AC *en bloc* with the nipple–areola complex and inferior segment. Nipple reconstruction is carried out by immediate reimplantation (after negative frozen section from the retroareolar tissue) or secondarily by tattooing.

Conservative surgery can be effective in treatment, but must produce a cosmetically acceptable breast[5].

Acknowledgements

Figure 1 was drawn by Gillian Lee.

References

1. Veronesi U, Salvadori B, Luini A *et al*. Conservative treatment of early breast cancer. *Ann Surg* 1990; **211**: 3.
2. Pezner RD, Patterson MP, Hill LR *et al*. Breast retraction assessment: an objective evaluation of cosmetic results of patients treated conservatively for breast cancer. *Int J Radiat Oncol Biol Phys* 1985; **11**: 575–8.
3. Yarnold JR. Factors affecting the cosmetic results and the scoring of normal tissue damage. In: Peckham M, Tobias JS, eds. *Primary Management of Breast Cancer: Alternatives to Mastectomy*. London: Edward Arnold, 1986: 114–30.
4. Pitanguy I. Surgical treatment of breast hypertrophy. *Br J Plast Surg* 1967; **20**: 78–85.
5. Veronesi U, Luini A, Andreoli C. *La Conservazione del Seno*. Milan: Edizione Sorbona, 1991: 9.

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Announcement

European Aeromedical Institute

On the initiative of the Medical Committee of the German Air Rescue (Deutsche Rettungsflugwacht), interested persons in the field of helicopter rescue work were invited to a first meeting in Frankfurt-am-Main on 8 September 1992 to discuss the setting up of an educational centre for air rescue in Europe and to found an advisory board for the European School for Air Rescue. After an amicable discussion concerning the different meanings of the European words ‘society’, ‘institute’, ‘centre’, ‘academy’ and ‘school’, the title was chosen as the European Aeromedical Institute Centre for Education, Information, Research and Supply with the abbreviation EURAMI unanimously accepted. The purposes of this organization will be mutual cooperation, establishment of standards, interchange of staff, protocols and data, documentation of all aeromedical services in Europe, training of personnel, teaching and scientific investigations, and the winning of European Parliamentary support for uniformly high standards of air rescue. Professor B. Domres was responsible for organizing this first meeting and, since he came from Tubingen, the future secretariat was agreed to be at nearby Stuttgart. Professor E. R. Steiner was chosen as the permanent Secretary but, although he was originally from Berlin, he would be working in Stuttgart. Before the first full meeting of EURAMI, correspondence should be with Professor Steiner, c/o Deutsche Rettungsflugwacht e.V., Echterdinger Straße 89, D-7024 Filderstadt 1, Germany. Telephone: 010 49 711 7007 414. All interested should contact him directly.

R. J. Earlam

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Outcome 5 years after 360° fundoplication for gastro-oesophageal reflux disease

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Forty patients with a mean age of 45 (range 22–65) years were operated on between 1982 and 1985 for gastro-oesophageal reflux disease with a short floppy 360° fundoplication. The results of the operation were determined by endoscopy, oesophageal manometry, ambulatory 24-h pH recording and symptom evaluation 6 months and 5 years after operation. These results were compared with findings in healthy controls. The median pressure in the lower oesophageal high-pressure zone was 13·3 (interquartile range (i.q.r.) 11·3–21·3) mmHg after 5 years, which did not differ significantly from the value at 6 months' follow-up or from that in controls. It was, however, significantly higher than the preoperative pressure. The median intra-abdominal length of the high-pressure zone was 1·7 (i.q.r. 1·3–2·3) cm after 5 years, significantly less than at 6 months but equal to control length. Measurement of the proportion of total time at pH < 4 at 5 years (median 0·2 (i.q.r. 0·0–0·6) per cent) and 6 months after operation revealed a significant reduction in acid reflux compared with preoperative values and normal controls. There was no significant difference in acid exposure between the two postoperative investigations. Endoscopy showed that 27 patients had no oesophagitis, three had erythema and three persistent Barrett's oesophagus 5 years after operation. Normal belching was possible in 22 patients and 18 experienced increased flatulence 5 years after fundoplication. An independent gastroenterologist found that the result was excellent in 16 patients, good in 16 and fair in four; two patients had a poor overall outcome of the operation. It is concluded that a 360° fundoplication provides good long-term control of reflux and that slight symptoms of overcompetence are common among patients operated on without affecting the overall result.

Gastro-oesophageal reflux disease (GORD) is the most common oesophageal disorder and is also the major indication for surgical therapy in benign oesophageal dysfunction. Fundoplication is the most widely used antireflux procedure. It has been shown to be a safe operation that provides good control of reflux at short-term follow-up[1]. In the present study the long-term effect of a 360° floppy fundoplication was determined. Results at 5 years were compared with those obtained before operation and 6 months afterwards, and with those found in healthy controls.

Patients and methods

The study group comprised 40 patients, ten women and 30 men, with a mean age of 45 (range 22–65) years at the time of operation. They were operated on for documented GORD resistant to medical treatment between 1982 and 1985. Early postoperative findings have already been reported[1]. The operations were performed by three senior surgeons. There were no patients with oesophageal stricture in the study, as the results of pH recording in such patients are unreliable. An additional five patients were operated on during this period but were not included in the short-term study because they refused to undergo follow-up investigations. Therefore, they have not been included in the present study.

The patients underwent symptom evaluation, upper gastrointestinal endoscopy, oesophageal manometry and 24-h oesophageal pH recording before operation, and 6 months and 5 years afterwards. At the 6-month follow-up three patients did not accept endoscopy. At the 5-year follow-up one patient did not agree to participate, one had died from a cause unrelated to the operation for reflux disease, and a total of five patients refused to undergo some of the examinations. For comparison, 50 volunteers were studied: these comprised 32 women and 18 men with a mean age of 39 (range 30–76) years with no previous symptoms of gastrointestinal disease and normal findings on endoscopy. They were recruited mainly from the hospital staff and their relatives, and were paid a minor sum for participation. They underwent oesophageal manometry and ambulatory 24-h oesophageal pH recording.

Table 1 *Grading of symptoms*

	Grade		
Symptom	1	2	3
Heartburn	Occasional episodes	Main reason for medical visit	Continuous, interferes with daily activities
Acid regurgitation	Occasional, after large meals	Predictable on position and straining	Episodes of pulmonary aspiration
Dysphagia	Occasional, short duration	Requires liquids to clear	Episodes of oesophageal obstruction requiring medical attention

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Symptom evaluation

Before the oesophageal tests, symptoms were assessed. A scoring system modified from that of DeMeester *et al.*[2] was used (*Table 1*). After operation an interview was conducted by a gastroenterologist unaware of the results of the investigations. The patients were asked specifically about reflux symptoms as well as the ability to vomit and belch and whether they had experienced increased flatus; they were also asked about any adverse effects experienced after the operation. The results of the operations were classified as excellent (complete recovery), good (major improvement with minor problems), fair (major improvement but still some significant symptoms or adverse effects) or poor (minor or no improvement or a deterioration).

Upper gastrointestinal endoscopy

Endoscopy was performed with flexible endoscopes after topical anaesthesia of the pharynx. Erythema, erosions or ulceration in the distal oesophagus were noted. Barrett's oesophagus was defined as circumferential gastric epithelium extending >3 cm up the tubular oesophagus. A hiatus hernia was diagnosed when the distance between the impressions of the diaphragmatic crura and the distal end of the tubular oesophagus exceeded 2 cm with the patient breathing quietly with a non-inflated stomach.

Oesophageal studies

Oesophageal manometry and ambulatory 24-h pH recording were performed as at the short-term follow-up[1], using the stationary pull-through technique with a three-lumen water-perfused catheter and ambulatory pH monitoring equipment (Synectics Medical, Stockholm, Sweden). Reflux was expressed as the percentage of total time that oesophageal pH was <4.

Table 2 *Symptoms reported before and after fundoplication*

Symptom	Grade*	Before operation	After operation 6 months	After operation 5 years
Heartburn†	0	4	37	31
	1	7	3	7
	2	13	0	0
	3	16	0	0
Acid regurgitation†	0	5	39	34
	1	17	1	3
	2	11	0	1
	3	7	0	0
Dysphagia	0	26	29	30
	1	12	7	7
	2	2	4	1
	3	0	0	0

*Grade 0 refers to patients without symptoms. †$P < 0·001$ (before *versus* 6 months and 5 years after operation); for all other comparisons, P not significant (χ^2 test, 3 d.f.)

Surgical procedure

The operation was performed abdominally through a left transverse or midline incision. The distal 5 cm of oesophagus was mobilized and the hiatus hernia, if present, reduced into the abdomen. The structures on the gastric lesser curve and fundus and the short gastric vessels were not divided. If the hiatus of the diaphragm was widened, it was narrowed by stitches in the crura dorsal to the oesophagus. A 36-Fr gastric tube was passed through the oesophagus into the fundus and the front wall of the latter passed dorsally to the right side of the oesophagus. Three non-absorbable sutures were placed from the greater curvature to the front wall of the oesophagus and to the gastric wall on the right side of the oesophagus. A 360° fundoplication 3 cm long was thus created, so that at least one finger could easily be passed through the fundoplication, which was not fixed to the diaphragm.

Statistical methods

Friedman's test, χ^2 analysis and the Mann–Whitney U test were used. $P \leq 0·05$ was considered significant. The investigation of the 50 normal subjects was approved by the university's ethical research committee.

Results

Symptoms

The effect of the operation on heartburn, acid regurgitation and dysphagia is shown in *Table 2*. The good control of heartburn and regurgitation seen at 6 months was also present 5 years after operation, but there were still patients with dysphagia at 5 years. The incidence of adverse effects such as an inability to belch (ten of 40 patients at 6 months, 16 of 38 at 5 years) and increased flatulence (16 of 40 at 6 months, 18 of 38 at 5 years) was not significantly changed after operation. The ability to vomit was increased at the 5-year follow-up (eight of 38 patients), but because no patient had tried to vomit 6 months after operation, and a number of patients had still not tried to do so at 5 years, the true ability to vomit is not known.

At the 5-year follow-up the outcome of the operation was classified as excellent in 16 patients, good in 16, fair in four and poor in two. Fifteen patients had the same overall result at the 6-month follow-up. The only patient with a poor result at the short-term follow-up had the same finding 5 years after operation, while the other patient with a poor result at the 5-year assessment had previously had a good overall result. The two patients with a fair outcome at 6 months were both improved and results in the four patients classified as fair at 5 years had been considered good or excellent at the 6-month follow-up.

Table 3 shows the results in patients with a fair or poor outcome. One of the patients with a fair overall result was found to have a paraoesophageal hernia, recurrent reflux on pH recording, and symptoms of heartburn and regurgitation. None of the other patients was classified as poor or fair due to recurrent reflux.

Table 3 *Patients with poor or fair overall results correlated with other findings 5 years after operation*

	Patient 1 (poor)	Patient 2 (poor)	Patient 3 (fair)	Patient 4 (fair)	Patient 5 (fair)	Patient 6 (fair)
Paraoesophageal or sliding hernia	No	No	Yes	No	No	No
Oesophagitis or Barrett's oesophagus	Yes	No	No	No	No	No
Lower oesophageal sphincter pressure (mmHg)	36	22	—	17	31	4
Intra-abdominal length of high-pressure zone (cm)	1·3	1·7	—	1·3	1·7	3
Reflux (percentage of time at pH < 4)	0·1	0	5·3	0	0	0
Heartburn grade*	1	1	1	0	0	1
Regurgitation grade*	0	0	1	0	0	1
Dysphagia grade*	0	1	0	0	0	0
Ability to belch	Yes	Yes	Yes	No	No	No
Ability to vomit	Yes	No	Yes	No	No	No
Increased flatulence	Yes	Yes	No	No	Yes	No

*For grading of symptoms see *Table 1*

Endoscopic findings (Table 4)

Three patients had grade 1 oesophagitis, none had grade 2 and three had Barrett's oesophagus at the 5-year examination. Two of the patients with Barrett's oesophagus had had the same findings before and 6 months after operation. The third patient was assessed at the 6-month examination as having grade 2 oesophagitis. All patients but one had a hiatus hernia before operation; all hernias had reduced at 6 months. At 5 years one recurrent hernia was found (paraoesophageal; *Table 3*). No patient had signs of wrap disruption at follow-up.

Table 4 *Results of endoscopy*

Endoscopic findings	Before operation ($n = 39$)	After operation 6 months ($n = 37$)	 5 years ($n = 33$)
No oesophagitis*†	5	32	27
Oesophagitis*†			
Erythema	5	0	3
Erosions or ulceration	25	3	0
Barrett's oesophagus*†	4	2	3

*$P < 0{\cdot}001$ (before *versus* 6 months and 5 years after operation); †P not significant (6 months *versus* 5 years after operation); χ^2 test, 3 d.f.

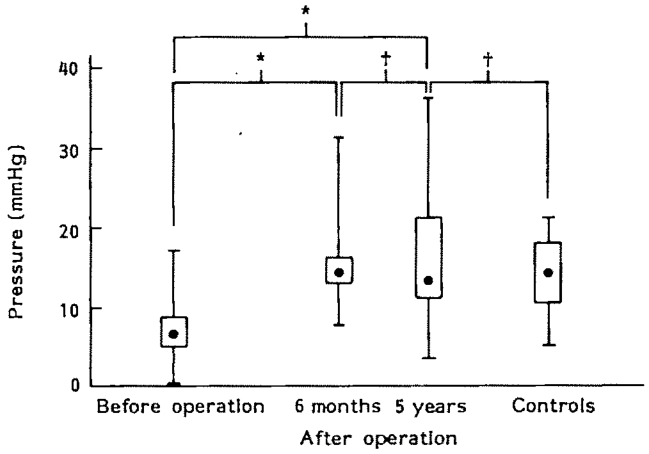

Figure 1 *Pressure in the lower oesophageal high-pressure zone. Values are median (range, bars; interquartile range, box).* *$P < 0{\cdot}001$; †P *not significant (Mann–Whitney* U *test)*

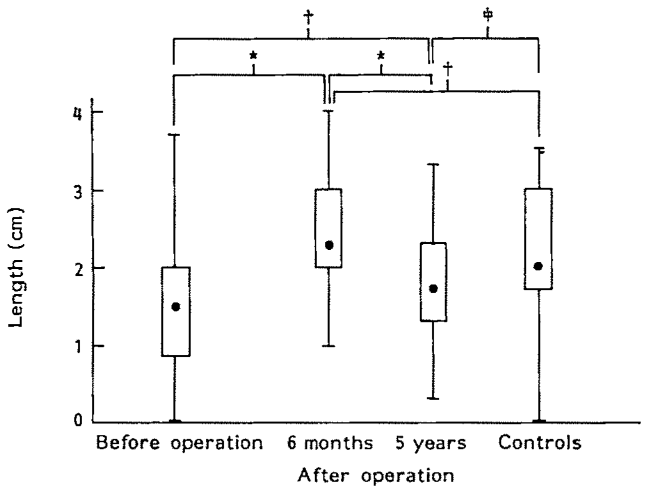

Figure 2 *Intra-abdominal length of the lower oesophageal high-pressure zone. Values are median (range, bars; interquartile range, box).* *$P < 0{\cdot}001$; †$P = 0{\cdot}03$; ‡P *not significant (Mann–Whitney* U *test)*

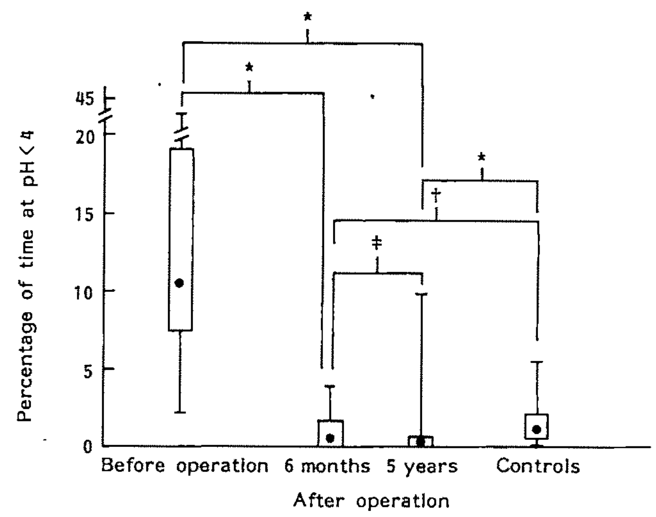

Figure 3 *Gastro-oesophageal reflux assessed by 24-h pH recording. Values are median (range, bars; interquartile range, box).* *$P < 0{\cdot}001$; †$P < 0{\cdot}01$; ‡P *not significant (Mann–Whitney* U *test)*

Manometry

Before operation the median pressure of the lower oesophageal high-pressure zone (HPZ) in patients was significantly lower than in normal subjects. After operation, both at 6 months and 5 years, there was a significant increase in pressure to normal levels (*Figure 1*).

The median intra-abdominal length of the HPZ was significantly lower in patients before surgery than in normal subjects (*Figure 2*). At 6 months after operation it had increased significantly and was greater than in normal subjects. However, after 5 years the intra-abdominal part of the HPZ had decreased to a length significantly shorter than at 6 months, although equal to normal (*Figure 2*).

pH recording

Ambulatory 24-h pH recording revealed a significant reduction in acid exposure of the lower oesophagus after fundoplication compared with results obtained before operation and in normal subjects (*Figure 3*). There was no significant difference in acid exposure between the two postoperative measurements. Three of the 36 patients who underwent pH testing 5 years after operation had acid reflux above the reference limit of this laboratory (pH < 4 for > 3·4 per cent of the total monitoring time). One of these was the patient with the paraoesophageal hernia, but the other two had no oesophagitis and had been assessed by the gastroenterologist as having a good operative outcome.

Discussion

In this study the long-term results of a short floppy 360° fundoplication were evaluated. The good overall results seen at short-term follow-up[1] were still present after 5 years.

Ambulatory 24-h pH recording is known to be the most sensitive method for revealing GORD[3]. The amount of acid reflux measured by ambulatory pH recording 5 years after operation was at the same low level as at 6 months. There was also a significant difference between the results obtained at 5 years and in normal subjects. This indicates that the antireflux control of the operation was still excellent after 5 years, with no tendency to an increase in reflux in these patients.

The resting pressure and intra-abdominal length of the lower oesophageal HPZ are known to be important components of the antireflux mechanism[4,5]. The present study has shown that the pressure in the HPZ at both 6 months and 5 years after operation was significantly increased compared with preoperative values. However, results also showed a significant decrease in the intra-abdominal length of the lower oesophageal HPZ at 5 years compared with 6 months after operation. The significance of this reduced intra-abdominal length is not fully clear, but the amount of acid reflux to the distal oesophagus was not affected.

Although no patient in this series had the gas-bloat syndrome, it has previously been reported[1] that the fundoplication is supercompetent: there is less reflux than in the control group and adverse effects occur such as an inability to belch and vomit, and increased flatus. We have suggested previously that these adverse effects may be due to some extent to the increased length of the intra-abdominal portion of the HPZ compared with that in normal subjects. The decrease in this length 5 years after operation to values not significantly different from those of normal subjects does not confirm this theory since there is no tendency for these adverse effects to diminish with time.

Despite the good control of gastro-oesophageal reflux obtained in this study, some patients have a less than perfect outcome, as judged by the gastroenterologist. *Table 3* shows the outcome in these patients, revealing signs of reflux in only one. It is unclear why the other five patients were not perfectly happy with the outcome of the operation; some reported slight symptoms or adverse effects, but these also occurred in patients who had a good or excellent result.

Endoscopy with mucosal biopsies has 100 per cent sensitivity and specificity for the identification of oesophagitis, but only 50–70 per cent sensitivity for the presence of GORD[6]. Furthermore, it has been proposed that patients with erythema in the distal oesophagus do not suffer reflux more than those with normal endoscopic findings, suggesting that erythema of the distal oesophagus should not be classified as oesophagitis[7–9]. Apart from the cases of Barrett's oesophagus, endoscopy showed only normal findings or grade 1 oesophagitis (erythema) 5 years after operation, confirming the good control of reflux provided by the fundoplication. The present results also confirm that Barrett's oesophagus seems to persist after antireflux surgery[10–12]. No endoscopic or histological signs of malignant transformation were noted.

Others[13,14] have reported a higher incidence of wrap disruption than in the present study. Even if the differences result from variation in operative technique, it is difficult to determine the exact mechanism.

This study has shown that it is possible to control reflux efficiently and safely with antireflux surgery and thus provide good long-term clinical results in patients with GORD.

References

1. Johnsson F, Joelsson B, Gudmundsson K, Floren C-H, Walther B. Influences of fundoplication on the antireflux mechanism. *Br J Surg* 1987; **74**: 1111–14.
2. DeMeester TR, Wang C-I, Wernly JA *et al.* Technique, indications, and clinical use of 24 hour esophageal pH monitoring. *J Thorac Cardiovasc Surg* 1980; **79**: 656–70.
3. Johnsson F, Joelsson B, Isberg P-E. Ambulatory 24 hour pH monitoring in the diagnosis of gastroesophageal reflux disease. *Gut* 1987; **28**: 1145–50.
4. Johnsson F, Joelsson B, Gudmundsson K. Determinants of gastro-oesophageal reflux and their inter-relationships. *Br J Surg* 1989; **76**: 241–4.
5. DeMeester TR, Wernly JA, Bryant GH, Little AG, Skinner DB. Clinical and *in vitro* determinants of gastroesophageal competence: a study of the principles of antireflux surgery. *Am J Surg* 1979; **137**: 39–46.
6. Mattox HE, Richter JE. Prolonged ambulatory esophageal pH monitoring in the evaluation of gastro-esophageal reflux disease. *Am J Med* 1990; **89**: 345–56.
7. Johnsson F, Joelsson B, Gudmundsson K, Greiff L. Symptoms and endoscopical findings in the diagnosis of gastro-esophageal reflux disease. *Scand J Gastroenterol* 1987; **22**: 714–18.
8. Johnson LF, DeMeester TR, Haggit RC. Endoscopic signs for gastro-esophageal reflux objectively evaluated. *Gastrointest Endosc* 1976; **22**: 151–5.
9. Sladen GE, Riddell RH, Willoughby JMT. Esophagoscopy, biopsy, and acid perfusion test in the diagnosis of reflux oesophagitis. *BMJ* 1975; i: 71–6.
10. DeMeester TR, Attwood SEA, Smyrk TC, Therkildsen DH, Hinder RA. Surgical therapy in Barrett's esophagus. *Ann Surg* 1990; **212**: 528–40.
11. Bremner CG. Barrett's oesophagus. *Br J Surg* 1989; **79**: 995–6.
12. Williamson WA, Ellis FH, Gibb SP, Shaian DM, Aretz HT. Effect of antireflux operation on Barrett's mucosa. *Ann Thorac Surg* 1990; **49**: 537–42.
13. O'Hanrahan T, Marples M, Banciewicz J. Recurrent reflux and wrap disruption after Nissen fundoplication: detection, incidence and timing. *Br J Surg* 1990; **77**: 545–7.
14. Breumelhof R, Smout AJPM, Schyns MWRJ, Bronzwaer PWA, Akkermans LMA, Jansen A. Prospective evaluation of the effects of Nisssen fundoplication on gastroesophageal reflux. *Surg Gynecol Obstet* 1990; **171**: 115–19.

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Cholecystectomy and oesophageal reflux: a prospective evaluation

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The effect of cholecystectomy on oesophageal function was examined prospectively. Of 37 patients studied, 17 (46 per cent) were still symptomatic 3–4 months after surgery. Thirteen patients (35 per cent) had abnormal oesophageal pH profiles before cholecystectomy, increasing to 27 (73 per cent) afterwards ($P < 0{\cdot}002$). *The mean(s.e.m.) DeMeester acid reflux score increased from 15·2(2·1) to 34·2(5·2)* ($P < 0{\cdot}001$) *after operation. Lower oesophageal sphincter function, as measured by the sphincter function index, was significantly reduced in the patients with abnormal pH profiles after operation* ($P < 0{\cdot}01$). *Mean(s.e.m.) supine gastric alkaline shift (proportion of time at pH > 4) increased from 9·2(2·0) to 17·7(3·7) per cent* ($P < 0{\cdot}02$) *and the incidence of gastritis from eight patients (22 per cent) to 23 (62 per cent)* ($P < 0{\cdot}001$). *These data suggest that cholecystectomy results in gastro-oesophageal reflux that appears to be related to compromised sphincter competence.*

The majority of patients who undergo cholecystectomy are satisfied with the operation and have no further symptoms, but a significant minority, between 20 and 50 per cent depending on the thoroughness of questioning and criteria for inclusion, have persistent or new symptoms[1–3]. Although such symptoms are usually ascribed to persistent biliary pathology, or to coexistent gastrointestinal pathology that was mistakenly attributed before operation to asymptomatic gallstones, evidence is now accumulating that gallbladder removal may itself have a direct role in symptom aetiology.

Cholecystectomy is associated with alterations in the composition[4,5] and dynamics[6,7] of bile secretion, predisposing to increased duodenogastric reflux of potentially more injurious bile. There is an increased incidence of duodenogastric reflux in patients with oesophageal symptoms[8], and patients who have undergone cholecystectomy have an increased incidence of oesophageal reflux and oesophagitis[9], although there are no prospective studies that have examined the effect of cholecystectomy on oesophageal function.

The aims of this study were to examine the effect of cholecystectomy on gastro-oesophageal reflux markers and to evaluate the link between oesophageal pathology and symptoms after cholecystectomy.

Patients and methods

All patients undergoing elective cholecystectomy in one unit between September 1990 and September 1991 were included. Only patients who had presented with clinical features of acute cholecystitis or biliary colic and had a diagnosis of symptomatic cholelithiasis supported by abdominal ultrasonography, oral cholecystography or both investigations were studied. Patients undergoing exploratory laparotomy, patients with acalculous cholecystitis and those requiring emergency surgery were excluded from the trial.

The aims and methods of the study were explained to the patients and informed consent obtained. The study was approved by the hospital's ethics committee.

Patients were studied before operation and again 3–4 months afterwards. A detailed questionnaire was completed on each patient by one of the authors (S.J.). All symptoms were documented regardless of severity. The questionnaire focused on the presence and type of symptoms experienced, and in particular on the presence of reflux symptoms.

Oesophageal function was evaluated by oesophageal manometry and 24-h oesophageal pH recording with simultaneous gastric pH monitoring. Upper gastrointestinal endoscopy was performed and biopsies were taken from the lower oesophagus and gastric antrum. Body-weight was recorded on admission and at each outpatient visit.

Oesophageal manometry

Stationary oesophageal manometry was performed using a four-lumen single-catheter assembly, with radially arranged side holes at 5-cm intervals. Each channel was perfused with distilled water at a rate of 0·6 ml/min using a low-compliance pneumohydraulic infusion system (Arndorfer, Greendale, Wisconsin, USA). The lower oesophageal sphincter (LOS) was identified using a station pull-through technique. Three manometric determinants of the LOS were measured: LOS pressure, and intra-abdominal and overall sphincter length. The sphincter function index was calculated as the product of the percentage of LOS exposed to abdominal pressure and LOS pressure[10].

Oesophageal body function was assessed as the mean amplitude and propagation of the pressure wave in response to ten wet swallows, each of a 5-ml bolus of water.

Oesophageal and gastric pH monitoring

Simultaneous gastric and oesophageal pH monitoring was carried out with a two-sensor antimony electrode catheter with sensors mounted 15 cm apart (Synectics Medical, Stockholm, Sweden). With this technique, the proximal sensor was placed 5 cm above and the distal sensor approximately 5 cm below the LOS. A silver–silver chloride external reference electrode was applied to the right upper anterior chest wall. The electrodes were connected to a dual-channel portable solid-state Digitrapper (Synectics) and the patients allowed home. They were required to keep a record of meals, symptoms and time spent supine and upright, but they continued normal activity. Data were analysed on a microcomputer using Gastrosoft software (Esophogram; Synectics).

Pathological acid reflux was defined with reference to the DeMeester acid score[11]. It was expressed as a composite score as described and was calculated automatically by the software. A threshold score of 15·0 was taken as the upper limit of normal.

Gastric pH was analysed for the percentage of time at pH > 4 for the total period and when in the upright and supine positions.

Upper gastrointestinal endoscopy

Upper gastrointestinal endoscopy was performed using a flexible endoscope in the sedated patient, given 5–10 mg intravenous midazolam after an overnight fast. The oesophagus, stomach and duodenum were examined and the presence of gross changes of gastritis or oesophagitis noted. Oesophagitis was graded using the Savary–Miller criteria[12]. Gastritis was recorded at endoscopy on the evidence of erosions, redness or friability of the mucosa. Bile in the oesophagus and stomach was also noted.

Biopsies were taken from the gastric antrum, 5 cm from the pylorus, and from the lower oesophagus, 5 cm from the cardia. Biopsies were

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considered supportive of gastritis if the mucosa was heavily infiltrated with acute or chronic inflammatory cells.

Statistical analysis

Results are expressed as mean(s.e.m.). Data were analysed using the Wilcoxon signed rank test for paired measurements. Attribute data were analysed by χ^2 or Fisher's exact test where appropriate.

Results

Patient details

Forty-five patients were recruited to the study, of whom eight refused postoperative investigations, leaving 37 for analysis. There were five men with a mean age of 43 (range 36–67) years and 32 women of mean age 45 (range 22–86) years.

Seventeen patients (46 per cent) were still symptomatic 3–4 months after cholecystectomy. For the purpose of this study they are described throughout as the 'symptomatic group'. The chief symptoms were heartburn and epigastric pain.

Fifteen patients complained of reflux symptoms after operation; symptoms were severe in seven. Only 11 of these patients had had reflux symptoms before operation. Of these 11 patients, three described their symptoms as severe before operation. After operation two continued to have severe symptoms and the third noted that symptoms had become milder. Eight patients had described mild reflux symptoms before operation and in this group symptoms became more severe in four, continued mild in three and disappeared in one patient. Of the six patients without reflux symptoms before operation, one developed severe reflux symptoms, four developed mild symptoms and one remained free of reflux symptoms after operation. This patient suffered postoperative epigastric pain.

Eleven patients complained of epigastric pain, which was mild in eight and moderately severe in three. Other symptoms were nausea in four patients, fatty food intolerance in four, indigestion in three, flatulence in three and right upper quadrant pain in two.

Two patients (5 per cent) had retained bile duct stones. Symptoms were right upper quadrant pain and indigestion in one, and epigastric pain, fatty food intolerance and heartburn in the other. Both had raised alkaline phosphatase levels and endoscopic retrograde cholangiography identified stones in the bile duct which were removed after sphincterotomy.

Oesophageal function

Thirteen (35 per cent) of the 37 patients undergoing cholecystectomy had gastro-oesophageal reflux before operation, increasing to 27 (73 per cent) after operation ($\chi^2 = 9·20$, 1 d.f., $P < 0·002$), as identified by a DeMeester acid reflux score >15. When the data were analysed as if the eight patients lost to follow-up were in the asymptomatic group, the increase in the incidence of reflux was still significant ($\chi^2 = 5·29$, 1 d.f., $P = 0·02$).

The mean(s.e.m.) DeMeester acid reflux score for the whole group increased from 15·2(2·1) to 34·2(5·2) ($P < 0·001$) after operation (*Table 1*). Fifteen of the 17 symptomatic patients (88 per cent) had reflux after operation compared with 12 of the 20 asymptomatic patients (60 per cent). When asymptomatic and symptomatic patients were compared after operation, there was a significant increase in the mean reflux score of the symptomatic group only (*Table 2*).

Table 1 *Changes in duodenogastric and gastro-oesophageal reflux markers following cholecystectomy*

	Before operation	After operation	χ^2	s.n.d.	P
Reflux*	13 (35)	27 (73)	9·20	—	<0·002†
Mean(s.e.m.) acid reflux score	15·2(2·1)	34·2(5·2)	—	3·63	<0·001‡
Mean(s.e.m.) lower oesophageal sphincter pressure (mmHg)	15·4(0·7)	14·3(0·9)	—	0·88	0·19‡
Mean(s.e.m.) percentage of supine time at gastric pH > 4	9·2(2·0)	17·7(3·7)	—	2·27	0·017‡
Oesophagitis*	8 (22)	19 (51)	5·83	—	0·016†
Gastritis*	8 (22)	23 (62)	10·88	—	<0·001†
Antral *Helicobacter pylori**	8 (22)	19 (51)	5·83	—	0·016†

*Values in parentheses are percentages. s.n.d., Standardized normal deviate with continuity correction; †1 d.f.; ‡Wilcoxon's signed rank test

Table 2 *Changes in duodenogastric and gastro-oesophageal reflux markers following cholecystectomy in symptomatic and asymptomatic patients*

	n	Before operation	After operation	χ^2	s.n.d.	P
Reflux*†						
Asymptomatic	20	9 (45)	12 (60)	0·40	—	0·53‡
Symptomatic	17	4 (24)	15 (88)	11·93	—	0·0006‡
Mean(s.e.m.) acid reflux score						
Asymptomatic	20	19·1(3·4)	23·5(4·0)	—	1·06	0·14§
Symptomatic	17	10·5(1·5)	46·7(9·5)	—	3·60	0·001§
Mean(s.e.m.) percentage of supine time at gastric pH > 4						
Asymptomatic	19	8·4(2·4)	10·1(2·9)	—	0·65	0·26§
Symptomatic	12	10·6(3·8)	29·6(7·3)	—	2·24	0·012§
Oesophagitis*						
Asymptomatic	20	5 (25)	6 (30)	0·00	—	1·00‡
Symptomatic	17	3 (18)	13 (76)	9·56	—	0·002‡
Gastritis*						
Asymptomatic	20	5 (25)	9 (45)	0·98	—	0·32‡
Symptomatic	17	3 (18)	14 (82)	11·77	—	0·0006‡

*Values in parentheses are percentages. s.n.d., Standardized normal deviate with continuity correction. †Patients with proven reflux on 24-h pH study. ‡1 d.f.; §Wilcoxon's signed rank test

Table 3 *Manometric measurements in patients with abnormal pH profile after operation*

	Before operation	After operation	P^*
Lower oesophageal sphincter pressure (mmHg)	11(1)	10(2)	0·06
Intra-abdominal sphincter length (mm)	24(3)	23(2)	0·48
Overall sphincter length (mm)	44(2)	45(2)	0·49
Sphincter function index	718(98)	507(115)	0·01

Values are mean(s.e.m.). *Wilcoxon's signed rank test

LOS pressure fell in 18 patients, remained unchanged in five and rose in 14. The mean(s.e.m.) pressure for the entire group decreased from 15·4(0·7) to 14·3(0·9) mmHg ($P = 0{\cdot}19$) (*Table 1*). No significant difference emerged between asymptomatic and symptomatic patients after operation.

When preoperative and postoperative values were compared in patients with an abnormal pH profile after operation, the fall in LOS pressure was not significant. The sphincter function index, however, did show a significant reduction ($P < 0{\cdot}01$). The results for all the parameters used to assess sphincter competence are given in *Table 3*.

The mean(s.e.m.) wave amplitude in the distal oesophagus was unchanged, at 51(4) before and 55(4) mmHg after surgery ($P = 0{\cdot}17$). No patient had an abnormally raised wave amplitude in the body of the oesophagus before operation, but four had abnormal pressures (mean >150 mmHg) after cholecystectomy.

Gastric pH monitoring

Gastric pH data were available for 31 patients both before and after operation, for the total period and for the duration of time in the upright and supine positions. The median postoperative gastric pH for the 24-h period was 2·6. Gastric alkaline shift (proportion of time at gastric pH > 4) increased significantly in the supine position, from a mean(s.e.m.) of 9·2(2·0) to 17·7(3·7) per cent ($P < 0{\cdot}02$) after surgery, but the change in the upright position, from 13·2(1·4) to 17·3(2·2) per cent ($P = 0{\cdot}067$), and for the total period, from 12·9(1·4) to 16·7(2·3) per cent ($P = 0{\cdot}07$), was not significant.

There was a greater postoperative rise in the symptomatic group, from a mean(s.e.m.) of 10·6(3·8) to 29·6(7·3) per cent ($P < 0{\cdot}01$), than in the asymptomatic group, from 8·4(2·4) to 10·1(2·9) per cent ($P = 0{\cdot}26$) (*Table 2*).

Endoscopic findings

Before operation, mild oesophagitis was present in four patients while one had free bile. After operation, superficial oesophagitis with minor erosions was present in seven patients.

Mild gastritis was recorded before operation in two patients and five had bile documented in the stomach. After operation, ten patients had bile lakes in the stomach, one had a lesser curve gastric ulcer, one had erosions and one had prepyloric and pyloric inflammation; four patients had gastritis alone.

Histology

In the oesophagus, eight (22 per cent) preoperative biopsy reports were consistent with reflux oesophagitis, increasing to 19 (51 per cent) after operation ($\chi^2 = 5{\cdot}83$, 1 d.f., $P = 0{\cdot}016$) (*Table 1*); 15 patients had grade 1 oesophagitis and four grade 2.

In the gastric antrum, preoperative biopsy identified acute or chronic inflammatory infiltrates in eight cases (22 per cent), increasing to 23 (62 per cent) after operation ($\chi^2 = 10{\cdot}88$, 1 d.f., $P = 0{\cdot}001$). *Helicobacter pylori* was identified on histological analysis in eight patients before operation, increasing to 19 after surgery ($\chi^2 = 5{\cdot}83$, 1 d.f., $P = 0{\cdot}016$). However, only three of these eight patients had gastritis before operation while 16 of the 19 with *H. pylori* after operation had gastritis.

Body-weight

Body-weight was recorded before and after operation in 29 of the patients. In 14 weight loss ≥1 kg occurred, in 12 weight gain ≥1 kg was recorded, while in three no change in weight was documented. Change in weight did not appear to correlate with either an increase in reflux or inflammatory change.

Discussion

This study has identified a significant increase in the incidence of gastro-oesophageal reflux and oesophagitis within 3 months of cholecystectomy. This confirms the findings of a previous retrospective study[9] of a significant increase in the incidence of oesophageal pathology in patients after cholecystectomy. Although a link between biliary and oesophageal pathology has long been recognized, this is the first prospective study to demonstrate objective reflux changes as a direct consequence of gallbladder removal.

The reason for these changes is unclear, although they may be attributed to the alterations in the dynamics and composition of bile release that follow cholecystectomy[4–7]. A significant increase in gastric alkaline shift was observed in the supine position after operation. A similar increase in duodenogastric reflux has been identified by others[4,5]. Duodenogastric reflux is a normal physiological event but it may assume greater significance after cholecystectomy when pyloric sphincter function is impaired[13,14]. Sandler *et al.*[15] have shown that tachykinins, which are in high concentration at the cardia, have a powerful effect on sphincter mechanisms and may have a role in this context. Others have shown that duodenogastric reflux is increased in patients with gallstones, regardless of the functional status of the gallbladder[16–18], and that this is increased further following cholecystectomy[6–8,18–20].

Basal oesophageal sphincter pressure alone did not show a significant reduction following cholecystectomy. Other mechanical factors that contribute to sphincter competence are overall and intra-abdominal sphincter length[21]. The sphincter function index showed a significant reduction in patients who had an abnormal pH profile after operation, suggesting that there is reduced sphincter competence after surgery. LOS incompetence, however, did not account for all of the reflux demonstrated. Patients with normal sphincter function and an abnormal pH profile may have reflux in the presence of progressive gastric dilatation[22], increased gastric pressure[22], persistent gastric reservoir[23] or gastric hypersecretion of acid[24].

While it may appear paradoxical that there was both an increase in gastric alkaline shift and in oesophageal acid reflux, the former was significant only in the supine position. The median pH in the stomach after operation for the 24-h period was 2·6, and such refluxate in the oesophagus would be interpreted as an acid rather than alkaline event. Consequently, the composition of the refluxate in this study may well be acid combined with alkaline duodenal refluxate. Dual-channel gastric and oesophageal pH monitoring is helpful in documenting the presence of duodenogastric reflux, which would otherwise be undetected in a single-channel oesophageal investigation.

Some 46 per cent of patients reviewed were still symptomatic at 3 months, an incidence similar to that found where patients have been studied prospectively and a thorough questionnaire completed[2,3], although in the majority of instances symptoms were mild. The cause of these symptoms cannot be ascertained in every case. In only two patients were the symptoms explained by retained stones in the bile duct. Of 15 patients with postoperative reflux symptoms, 14 had reflux confirmed on pH monitoring. The one patient who did not have acid reflux had a high alkaline reflux score and histological gastritis. Of the 14 patients with reflux on pH monitoring, 11 had oesophagitis on histological analysis, but 12 also had gastritis, three had nutcracker oesophagus and two had retained common bile duct stones. It is hard to escape the conclusion that most of these problems were due to the cholecystectomy.

In conclusion, many of the symptoms that persist following cholecystectomy appear to have an oesophageal origin. It is suggested that all patients presenting with biliary symptoms but without documented acute cholecystitis should undergo full upper gastrointestinal investigations with oesophagogastroduodenoscopy, biopsy and pH monitoring to exclude oesophageal pathology. Discovery of reflux before operation should prompt consideration of antireflux surgery in addition to cholecystectomy.

It is clear that cholecystectomy is not innocuous. It results in physiological disturbance of the upper gastrointestinal tract that may in the long term have undesirable sequelae in the oesophagus and stomach. Retention of the functioning gallbladder or simultaneous antireflux surgery may be desirable in selected patients to avoid these sequelae.

References

1. Moody FG. The post-cholecystectomy syndrome. In: Moody F, Carey L, Jones S, Kelly K, Nahrwold D, Skinner D, eds. *Surgical Treatment of Digestive Disease.* Chicago: Year Book, 1986: 296–305.
2. Ros E, Zambon D. Postcholecystectomy symptoms. A prospective study of gallstone patients before and two years after surgery. *Gut* 1987; **28**: 1500–4.
3. Bates T, Ebbs SR, Harrison M, A'hern RP. Influence of cholecystectomy on symptoms. *Br J Surg* 1991; **78**: 964–7.
4. Malagelada JR, Go VLW, Summerskill WHJ, Gamble WS. Bile acid secretion and biliary bile acid composition altered by cholecystectomy. *Dig Dis Sci* 1973; **18**: 455–9.
5. Pomare EW, Heaton KW. The effect of cholecystectomy on bile salt metabolism. *Gut* 1973; **14**: 753–62.
6. Lorusso D, Pezzolla F, Montesani C *et al.* Duodenogastric reflux and gastric histology after cholecystectomy with or without sphincteroplasty. *Br J Surg* 1990; **77**: 1305–7.
7. Brough WA, Taylor TV, Torrance HB. The effect of cholecystectomy on duodenogastric reflux in patients with previous peptic ulcer surgery. *Scand J Gastroenterol Suppl* 1984; **19**: 255–6.
8. Kaye MD, Showalter JP. Pyloric incompetence in patients with symptomatic gastroesophageal reflux. *J Lab Clin Med* 1974; **83**: 198–206.
9. Walsh TN, Jazrawi S, Byrne PJ, Hennessy TPJ. Cholecystectomy and gastro-oesophageal reflux. *Br J Surg* 1991; **78**: 753 (Abstract).
10. Byrne PJ, Stuart RC, Lawlor P, Walsh TN, Hennessy TPJ. A new oesophageal sphincter function index. *Eur Surg Res* 1991; **23**(Suppl 1): 47.
11. DeMeester TR. Prolonged esophageal pH monitoring. In: Read NW, ed. *Gastrointestinal Motility: Which Test?* Petersfield, UK: Wrighton Biomedical Publishing, 1989: 41–52.
12. Savary M, Miller G. The esophagus. In: Savary M, Miller G, eds. *Handbook and Atlas of Endoscopy.* Solothurn, Switzerland: Verlag–Gassman, 1978: 119–205.
13. Johnson AG. Pyloric function and gallstone dyspepsia. *Br J Surg* 1972; **59**: 449–54.
14. Capper WM, Butler TJ, Kelly JO, Gibson MJ. Gallstones, gastric secretion and flatulent dyspepsia. *Lancet* 1967; **i**: 413–15.
15. Sandler AD, Maher JW, Weinstock JV *et al.* Tachykinins in the canine gastroesophageal junction. *Am J Surg* 1991; **161**: 165–70.
16. Svensson JO, Gelin J, Svanvik J. Gallstones, cholecystectomy, and duodenogastric reflux of bile acid. *Scand J Gastroenterol* 1986; **21**: 181–7.
17. Cabrol J, Navarro X, Simo-Deu J, Segura R. Evaluation of duodenogastric reflux in gallstone disease before and after simple cholecystectomy. *Am J Surg* 1990; **160**: 283–6.
18. Cranford CA, Kennedy NSJ, Sutton D, Cuschieri A. The relationship between enterogastric reflux of bile and gallbladder function. *Am J Gastroenterol* 1987; **82**: 972.
19. Brown TH, Walton G, Cheadle WG, Larson GM. The alkaline shift in gastric pH after cholecystectomy. *Am J Surg* 1989; **157**: 58–65.
20. Larusso D, Misciagna G, Mangini V *et al.* Duodenogastric reflux of bile acids, gastrin and parietal cells, and gastric acid secretion before and 6 months after cholecystectomy. *Am J Surg* 1990; **159**: 575–8.
21. Zaninotto G, DeMeester TR, Schwizer W, Johansson K-E, Cheng S-C. The lower esophageal sphincter in health and disease. *Am J Surg* 1988; **155**: 104–11.
22. Bonavina L, Evander A, DeMeester TR *et al.* Length of the distal esophageal sphincter and competency of the cardia. *Am J Surg* 1986; **151**: 25–34.
23. Malagelada JR. Physiological basis and clinical significance of gastric emptying disorders. *Dig Dis Sci* 1979; **24**: 657–61.
24. Boesby S. Relationship between gastroesophageal acid reflux, basal gastroesophageal sphincter pressure and gastric acid secretion. *Scand J Gastroenterol* 1977; **12**: 547–51.

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Gastric remnant cancer as a metachronous multiple lesion

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The pathological characteristics and natural history of 35 gastric remnant cancers after partial gastrectomy for a malignant condition and 16 gastric cancers after gastrectomy for benign conditions were compared. Gastric remnant cancer following malignant disease was characterized by a well defined rather than diffuse appearance (in 43 versus *12 per cent of gastric remnant cancers after benign conditions,* $P < 0{\cdot}05$*), location away from the anastomosis (83* versus *25 per cent,* $P < 0{\cdot}05$*) and a shorter interval after the first operation (5–14* versus *≥20 years,* $P < 0{\cdot}01$*). The 15- and 16-year survival rates appeared to be worse for gastric remnant cancer after malignant than after benign disease, but there was no statistically significant difference between the two groups in a generalized Wilcoxon test. In the former, direct invasion to adjacent organs was frequently observed. These findings suggest that gastric remnant cancer after gastrectomy for malignancy may be a metachronous multiple lesion, while that following benign disease may occur as a new cancer caused by the partial gastrectomy. To improve the survival of patients with cancer after gastrectomy for malignancy, a rational extended operation may be useful.*

There have been many reports of cancer developing in the stomach remnant after partial gastrectomy and patients who have undergone this operation are considered to be a high-risk group for gastric carcinoma. These cancers often develop at the site of anastomosis >20 years after operation for benign disease[1]. In this hospital there has been an increase in the number of patients whose cancers were found in the stomach remnant after partial gastrectomy for malignant disease (ten cases during 1961–1974 *versus* 25 for 1975–1986). In contrast, in this time only 16 cases[2] have been seen after partial gastrectomy for benign disease. Such cancers in the gastric remnant seem likely to increase due to the rise in cases of early gastric cancer (the proportion of early gastric cancer was >50 per cent in 1988 in this hospital[3]).

Patients and methods

A total of 2414 patients underwent partial gastrectomy for gastric cancer from 1961 to 1986. Follow-up was at least 5 years (maximum 30 years). Cancer in the gastric remnant after partial gastrectomy for a malignant condition was found 5 or more years after operation in 35 patients (29 men, six women; sex ratio 4·8:1). The mean age at which cancer was found in the stomach remnant was 62 (range 35–86) years. The interval from first operation to second was 5–9 years in 19 patients, 10–14 years in 12, 15–19 years in three and ≥20 years in one.

In contrast, 16 patients developed cancer in the stomach remnant after partial gastrectomy for benign disease. This figure includes patients who underwent the first operation in another hospital. These two groups of patients with gastric remnant cancer were compared for macroscopic and histological tumour type, site of development, results of treatment and relative risk.

The relative risk of developing cancer in the gastric remnant after malignancy was calculated using a program derived from that of Monson[4] to suit the cancer registry in Osaka. The period of observation began at the first operation for stomach cancer and ended at either operation for gastric remnant cancer following malignancy, diagnosis of this disease, or on 31 December 1989. The sex, age and 5-year incidences for cancer among Osaka residents were applied to the appropriate person-years to obtain the expected numbers of cases of gastric remnant cancer after malignancy. These were compared with the relative risk of cancer in the stomach remnant after gastrectomy for benign disease calculated in Kyushu, Japan[5].

Statistical analysis

χ^2 analysis and Fisher's exact test were used to compare frequencies. Means were compared by Student's *t* test. The Kaplan–Meier method was used to prepare survival curves and the log rank test, *Z* test and generalized Wilcoxon test employed for statistical analysis.

Results

There were 51 cases of gastric remnant cancer: 31 were diagnosed radiologically and 20 by endoscopy. In nine cases the cancer could not be detected radiologically but was detected by endoscopy. Two-thirds of cases of cancer after gastrectomy for malignancy were already advanced despite careful follow-up.

Table 1 shows the interval between partial gastrectomy and development of gastric remnant cancer. The interval for originally benign conditions was significantly longer than that for originally malignant disease ($P < 0{\cdot}01$).

Tumours were resected in 29 of 35 cases (83 per cent) of remnant cancer after malignancy and in 14 of 16 cases (88 per cent) after initially benign disease. Tumour node metastasis (TNM) stage for resected tumours is shown in *Table 2*. There was no statistical difference between the two groups in T and N.

Histopathological classification is shown in *Table 3*. Gastric

Table 1 *Details of patients with gastric remnant cancer developing after partial gastrectomy for initially benign or malignant disease*

	Initial disease		
	Malignant	Benign	*P*
Sex ratio (F:M)	6:29	1:15	n.s.†
Mean(s.d.) age (years)	62(11)	62(9)	n.s.‡
Interval between operations (years)*			
5–9	19	0	<0·01§
10–14	12	5	
15–19	3	1	
≥20	1	10	

*Interval between partial gastrectomy and operation for gastric remnant cancer. n.s., Not significant. †Fisher's exact test; ‡Student's *t* test; §$\chi^2 = 26{\cdot}9$, 3 d.f., $P < 0{\cdot}01$

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Table 2 *Tumour node metastasis classification determined in patients undergoing resection for gastric remnant cancer*

	Initial disease	
Classification	Malignant ($n = 29$)	Benign ($n = 14$)
T_{is}	10 (34)	3 (21)
T_1	2 (7)	1 (7)
T_2	1 (3)	1 (7)
T_3	10 (34)	6 (43)
T_4	6 (21)	3 (21)
N_0	11 (38)	4 (29)
$N_{1/2}$	10 (34)	7 (50)
$>N_2$	8 (28)	3 (21)

Values in parentheses are percentages. Differences between groups were not significant (χ^2 test)

Table 3 *Histopathological classification of gastric remnant tumours*

	Initial disease	
	Malignant ($n = 35$)	Benign ($n = 16$)
Macroscopic*		
Well defined	15 (43)	2 (12)
Early (includes I and IIa)	10 (29)	1 (6)
Advanced (includes Borrmann types I and II)	5 (14)	1 (6)
Diffuse	20 (57)	14 (88)
Early (includes IIb, IIc and III)	1 (3)	2 (12)
Advanced (includes Borrmann types III and IV)	19 (54)	12 (75)
Microscopic*		
Differentiated (includes papillary and tubular adenocarcinoma)	23 (66)	5 (31)
Undifferentiated (includes poorly differentiated adenocarcinoma and signet-ring cell carcinoma)	12 (34)	11 (69)

Values in parentheses are percentages. *$P < 0{\cdot}05$ (χ^2 test)

remnant cancer after gastrectomy for malignancy was classified into four types: well defined early cancer[6] (I and IIa) in ten patients (29 per cent); well defined advanced cancer (Borrmann types I and II) in five (14 per cent); infiltrative early cancer (IIb, IIc and III) in one (3 per cent); and infiltrative advanced cancer (Borrmann types III and IV) in 19 (54 per cent). The incidence of the well defined types was higher in cancer for initially malignant (43 per cent) than initially benign (12 per cent) conditions ($P < 0{\cdot}05$).

Gastric remnant cancer after gastrectomy for malignancy was classified into differentiated types[6] (papillary and tubular) in 23 cases (66 per cent) and undifferentiated types (poorly differentiated and signet-ring cell carcinoma) in 12 (34 per cent). The incidence of the differentiated types was higher in initially malignant than in initially benign disease (66 *versus* 31 per cent, $P < 0{\cdot}05$).

Remnant cancer after malignancy was located at the site of anastomosis in six patients (17 per cent) and in other regions in 29 (83 per cent) (*Figure 1*). That after gastrectomy for benign conditions was more frequently (75 per cent) ($P < 0{\cdot}001$) found at the site of anastomosis (*Figure 1*).

Gastric resection was possible in 29 patients (83 per cent) with initial malignancy and in 14 (88 per cent) with initially benign disease. The remainder had peritoneal metastasis in six patients (initial condition malignant in five, benign in one), liver metastasis in one (malignant) and para-aortic lymph node metastases in one (benign). All resected cases underwent total gastrectomy and the following procedures in combination: left thoracotomy for oesophageal invasion (malignant, four; benign, two), splenectomy without distal pancreatectomy (11, seven), splenectomy with distal pancreatectomy (15, seven), transverse colectomy (five, five) and liver resection for direct invasion (one, one). As a result, direct invasion to adjacent organs was confirmed in six patients with gastric remnant cancer after malignancy (pancreas, four; colon, three; liver, one; diaphragm, one) and in three after benign disease (pancreas, two; liver, one). Survival rate is shown in *Figure 2*.

Dissection of the lymph nodes was performed to include the right cardia, left cardia, lesser curvature and greater curvature node groups only in nine patients (five malignant, four benign), these groups and those at the left gastric artery, common hepatic, coeliac trunk, splenic hilum and splenic artery in 17 (12, five), and a wider dissection than this in 14 (nine, five). The incidence of lymph node metastasis was compared in the two groups (*Table 4*). There was no significant difference in the distribution of lymph node metastases.

The relative risk of gastric remnant cancer after malignancy in Osaka was 0·52 in men and 0·77 in women. This was higher than the relative risk of gastric remnant cancer after benign disease previously reported in Kyushu[5] (0·30 in men and 0·63 in women).

In gastrectomy for malignancy, the survival rates with gastric remnant cancer were 37 per cent (ten patients) at 5 years, 28 per cent (five) at 10 years and 20 per cent (two) at 15 years. In cancer following gastrectomy for benign conditions, the 5-, 10- and 15-year survival rates were constant at 50 per cent (eight, five and three patients respectively). There was no statistically significant difference between the two groups with the generalized Wilcoxon test. The causes of early death (within

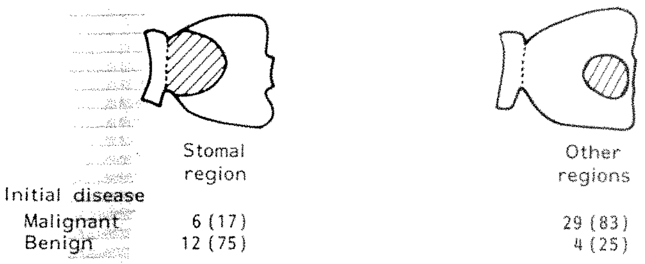

Figure 1 *Location of gastric remnant cancers developing after partial gastrectomy for a malignant or benign condition. Values in parentheses are percentages. There was a statistically significant difference between the frequency of tumours at the anastomosis in the two groups* (P < 0·001, χ^2 *test*)

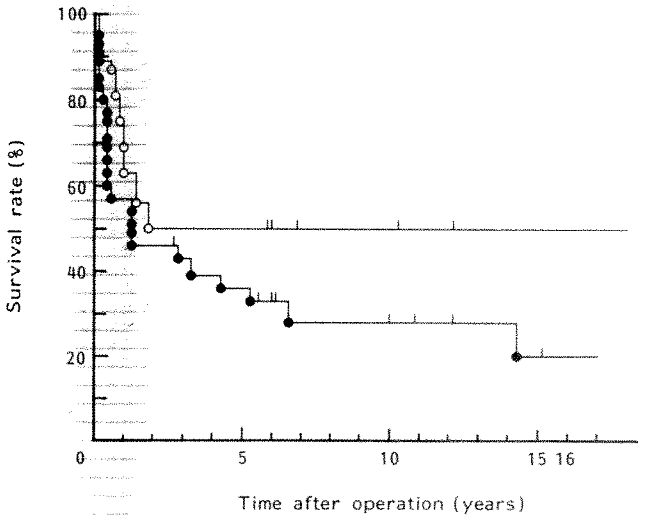

Figure 2 *Survival of patients with gastric remnant cancer developing after partial gastrectomy for initially malignant (●, died; ⊥, lived) or benign (○, died; ⊥, lived) conditions. Six and two patients respectively did not undergo resection. Rates are significantly different* (P < 0·05, Z *test) at 15 and 16 years, although with a generalized Wilcoxon test no significant difference between the groups was found*

Table 4 *Lymph node metastasis in patients with gastric remnant cancer*

Lymph node station	Initial disease Malignant ($n = 29$)	 Benign ($n = 14$)
Right cardia	3 (10)	4 (29)
Left cardia	9 (31)	4 (29)
Lesser curvature	2 (7)	5 (36)
Greater curvature	7 (24)	5 (36)
Coeliac	0 (0)	2 (14)
Splenic hilum	4 (14)	2 (14)
Splenic artery	3 (10)	3 (21)
Jejunal	2 (7)	1 (7)

Values in parentheses are percentages. Differences in distribution of metastases between the two groups were not significant (χ^2 test)

1 year) in initially malignant cases after curative surgery were myocardial infarction in two patients, anastomotic leakage in one, pneumonia in one and cerebral haemorrhage in one; there were no signs of recurrence. The 5-, 10- and 15-year cancer-specific survival rates were all 58 per cent after gastrectomy for benign disease and 42, 40 and 40 per cent respectively after initial malignancy. The cancer-specific survival rates in the two groups were also not significantly different.

Discussion

There have been many reports of cancer of the gastric remnant developing after partial gastrectomy for benign disease[1,7,8] but few of cancers after partial gastrectomy for malignant tumours[9]. The reasons for this are thought to be early death from recurrence or an inability to perform adequate follow-up studies. Some authors have reported that the relative risk of gastric remnant cancer after benign conditions is high in Northern Europe[7,8], while the relative risk of this form of cancer in Japan is low[5]. In this study, the relative risk of gastric remnant cancer after initial malignancy is higher than that after initial benign disease in Japan. In recent years the frequency of operation for early gastric cancer has increased and recurrence is seldom seen after operation in these cases[10]. Thus, there appears to be a new type of gastric remnant cancer in patients who have survived for a long period after partial gastrectomy for malignant disease.

Diagnosis of gastric remnant cancer is difficult and such lesions are often found at an advanced stage after the appearance of symptoms. Offerhaus *et al.*[11] were able to diagnose early-stage cancer by biopsy of the anastomosis during periodic endoscopic examinations after operation. Orlando and Welch[12] also reported the usefulness of endoscopic examination.

The cause of gastric remnant cancer after gastrectomy for benign conditions may be reflux of bile or intestinal fluid[13]. Investigations using experimental anastomosis have shown that reflux of such fluid is capable of inducing cancer at the anastomosis[14,15]. In contrast, remnant cancer after initial malignancy has many characteristics of multifocal cancer developing at different times, rather than a lesion caused by irritation from reflux. It develops within a short time (in this study, 5–14 years after the first operation compared with ⩾20 years for cancer after initially benign conditions) and most lesions are located at sites away from the anastomosis.

Adhesions surrounding the stomach remnant are often more severe after gastrectomy for malignant than benign disease because of the more extensive lymph node dissection. After such extended lymphadenectomy, a new pathway of spread for cancer cells to surrounding organs and peritoneum may be available. Some cases of gastric remnant cancer following initial malignancy were invasive and unexpectedly widespread, and a left upper abdominal evisceration[16] was required in these patients to resect the wider region including the whole stomach and surrounding organs (spleen, pancreatic body and tail, left adrenal gland, gallbladder and transverse colon).

After partial gastrectomy for gastric cancer, we recommend endoscopic examination, including biopsy, at least once a year. The endoscopist should carefully inspect not only the site of anastomosis but also other regions.

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References

1. Klarfeld J, Resnick G. Gastric remnant carcinoma. *Cancer* 1979; **44**: 1129–33.
2. Sasako M, Maruyama K, Kinoshita T, Okabayashi K. Surgical treatment of carcinoma of the gastric stump. *Br J Surg* 1991; **78**: 822–4.
3. Sano T, Okuyama Y, Kobori O *et al.* Early gastric cancer. Endoscopic diagnosis of depth of invasion. *Dig Dis Sci* 1990; **35**: 1340–4.
4. Monson RR. Analysis of relative survival and proportional mortality. *Comput Biomed Res* 1974; **7**: 325–32.
5. Tokudome S, Kono S, Ikeda M *et al.* A prospective study on primary gastric stump cancer following partial gastrectomy for benign gastroduodenal disease. *Cancer Res* 1984; **44**: 2208–12.
6. Japanese Research Society for Gastric Cancer. The general rules for the gastric cancer study in surgery and pathology. *Jpn J Surg* 1981; **11**: 127–39.
7. Viste A, Bjornestad E, Opheim P *et al.* Risk of carcinoma following gastric operations for benign disease. A historical cohort study of 3470 patients. *Lancet* 1986; **ii**: 502–5.
8. Lundegardh G, Adami HO, Helmick C, Zack M, Meirik O. Stomach cancer after partial gastrectomy for benign ulcer disease. *N Engl J Med* 1988; **319**: 195–200.
9. Iwanaga T, Koyama H, Imaoka S, Furukawa H, Hiratsuka M, Ogawa A. Primary gastric cancers of patients with partially resected stomach and lately heterochronous second cancer in the residual stomach. *Surgical Therapy* (*Japan*) 1987; **57**: 266–70.
10. Furukawa H, Hiratsuka M, Kameyama M *et al.* Treatment for early gastric cancer. *Surgical Therapy* (*Japan*) 1985; **52**: 389–94.
11. Offerhaus GJA, Stadt J, Huibregtse K, Tersmette A, Tytgat GNJ. The mucosa of the gastric remnant harboring malignancy. Histologic findings in the biopsy specimens of 504 asymptomatic patients 15 to 46 years after partial gastrectomy with emphasis on nonmalignant lesions. *Cancer* 1989; **64**: 698–703.
12. Orlando R, Welch JP. Carcinoma of the stomach after gastric operation. *Am J Surg* 1981; **141**: 487–91.
13. Domellof L, Janunger K-G. The risk of gastric carcinoma after partial gastrectomy. *Am J Surg* 1977; **134**: 581–4.
14. Nishidoi H, Koga S, Kaibara N. Possible role of duodenogastric reflux on the development of remnant gastric carcinoma induced by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in rats. *J Natl Cancer Inst* 1984; **72**: 1431–5.
15. Kobori O, Shimizu T, Maeda M *et al.* Enhancing effect of bile acid on stomach tumorigenesis induced by *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in Wistar rats. *J Natl Cancer Inst* 1984; **73**: 853–61.
16. Furukawa H, Hiratsuka M, Iwanaga T. A rational technique for surgical operation on Borrmann type 4 gastric carcinoma: left upper abdominal evisceration plus Appleby's method. *Br J Surg* 1988; **75**: 116–19.

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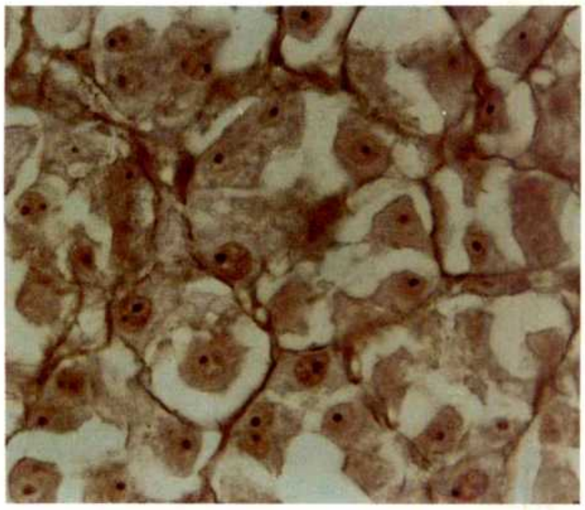

Figure 1 *Normal gastric mucosa nucleolar organizing regions stained with silver nitrate. (Original magnification × 1250)*

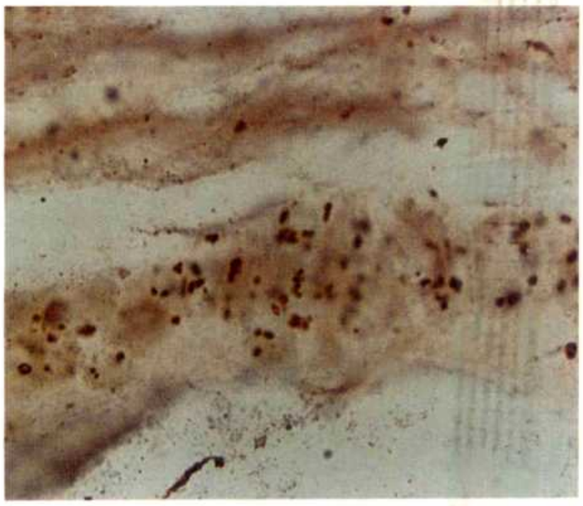

Figure 2 *Adenocarcinoma, showing most cells containing silver-stained nucleolar organizing regions. (Original magnification × 1250)*

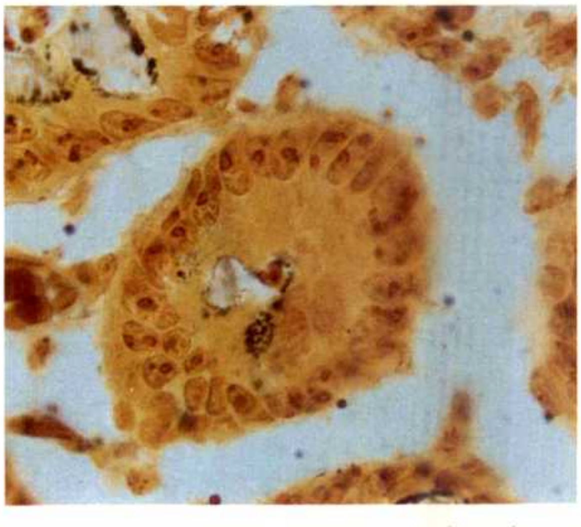

Figure 3 *Intestinal metaplasia, showing one to three silver-stained nucleolar organizing regions per nucleus. (Original magnification × 1250)*

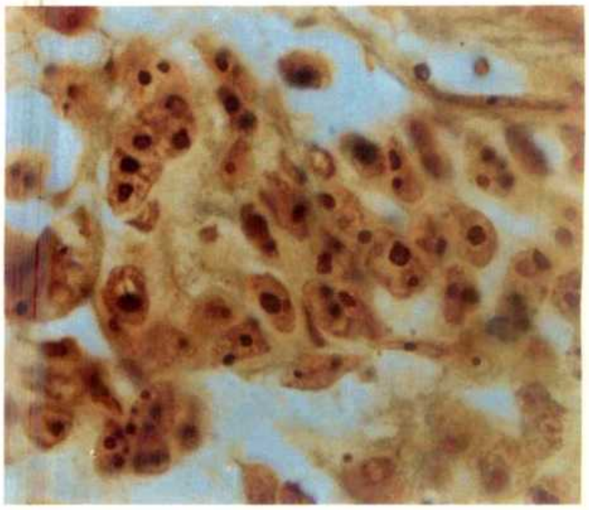

Figure 4 *Dysplasia, showing one to four silver-stained nucleolar organizing regions per nucleus. (Original magnification × 1250)*

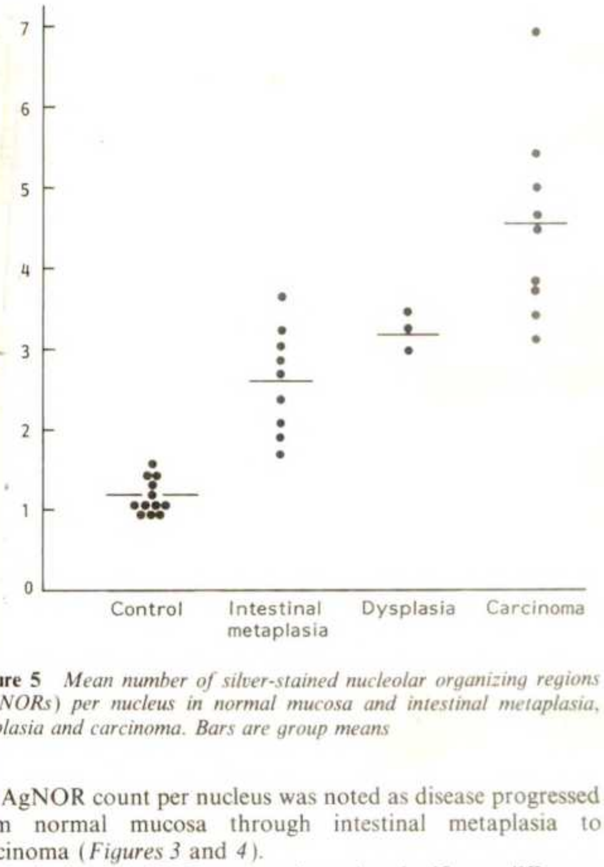

Figure 5 *Mean number of silver-stained nucleolar organizing regions (AgNORs) per nucleus in normal mucosa and intestinal metaplasia, dysplasia and carcinoma. Bars are group means*

the AgNOR count per nucleus was noted as disease progressed from normal mucosa through intestinal metaplasia to carcinoma (*Figures 3* and *4*).

Analysis of AgNOR counts showed a significant difference between normal epithelium and adenocarcinoma, intestinal metaplasia and dysplasia ($P < 0{\cdot}001$). There was, however, a considerable overlap among carcinoma, intestinal metaplasia and dysplasia ($P > 0{\cdot}1$) (*Figure 5*).

Discussion

Experimentally induced gastric cancer after duodenogastric reflux has been studied by others. Morgenstern[16] operated on rats and administered 20-methylcholanthrene after gastroenterostomy; at the end of the study, tumour occurred in 64 per cent of animals. Langhans *et al.*[5] used five techniques, one of which was gastroenterostomy without resection. Tumour incidence in this study was 71 per cent. Mason[7] investigated the role of duodenogastric reflux in the pathogenesis of gastric cancer and showed that reflux was implicated in gastric

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Nucleolar organizing regions in the operated rat stomach: relationship to metaplasia, dysplasia and carcinoma

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This study investigated the role of duodenogastric reflux in rats after antecolic gastrojejunostomy. At the end of the study, adenocarcinoma was present in 43 per cent, dysplasia in 14 per cent and intestinal metaplasia in 43 per cent of animals. No such changes were found in control rats. A technique for silver staining nucleolar organizing regions (AgNORs) was applied to these lesions and to the control group. The AgNOR count gradually increased from normal gastric mucosa to carcinoma. This technique demonstrated differences in AgNOR count between normal mucosa and other lesions (adenocarcinoma, dysplasia, intestinal metaplasia) ($P < 0{\cdot}001$). There was, however, considerable overlap among adenocarcinoma, dysplasia and metaplasia ($P > 0{\cdot}1$).

Peptic ulcer surgery may predispose to the subsequent development of gastric cancer[1,2], although this remains controversial[3] and the aetiological mechanisms are not fully understood. Some possible causes are duodenogastric reflux[4–7], hypochlorhydria[8,9] and overgrowth of nitrate-reducing bacteria[3].

Atrophic gastritis, intestinal metaplasia and dysplasia are all associated with gastric carcinogenesis[10,11] and gastric epithelial proliferation accompanies these premalignant mucosal changes[12]. Most gastric cancers appear to evolve through a progression of changes from chronic atrophic gastritis to intestinal metaplasia, dysplasia and finally carcinoma[13]. Although there is basic agreement on the lesions themselves, the transition periods for each stage of the premalignant process are largely unknown.

The main problem in routine diagnosis is interpretation of a biopsy showing chronic atrophic gastritis, intestinal metaplasia or dysplasia. The present study attempted to define further the precursor lesions of gastric carcinoma by quantitative evaluation of nucleolar organizing regions (NORs).

NORs are loops of DNA in the nuclei of cells that possess ribosomal RNA genes. These genes are transcribed by RNA polymerase. The silver technique for identifying such regions (AgNORs) stains NOR-associated proteins and reveals changes in NOR distribution. For example, an increased number of NORs is associated with more active ribosomal RNA gene transcription. Therefore it is expected that malignant epithelial cells would have higher AgNOR counts per nucleus than their non-neoplastic counterparts. NORs are located[14] on five acrocentric chromosomes (nos 13, 14, 15, 21, 22) and can be readily visualized as black dots in the nuclei by the silver staining method. The technique is based on argyrophilia of NOR-associated proteins and can be performed at room temperature on paraffin-embedded tissue. Although the nature of these NOR-associated proteins is not fully understood, it appears that AgNOR numbers reflect nuclear activity or malignant potential.

Materials and methods

This experimental study was performed in the Istanbul University Centre for Experimental Medical Research and Application. The animals were male Wistar rats, weighing between 220 and 280 g. The rats were subjected to either a sham operation ($n = 12$) or gastroenterostomy without resection to allow duodenogastric reflux ($n = 21$). (In total, 30 rats were operated on for duodenogastric reflux; nine (30 per cent) died after operation and the surviving 21 were included in the study.) All operations were performed under ether anaesthesia. Sham-operated animals underwent laparotomy with handling of the stomach and jejunum and acted as a control. In the other group, an antecolic gastroenterostomy without gastric resection was performed. Continuous 5/0 silk sutures were used for all anastomoses. Some 45 weeks after operation all rats were killed and submitted to autopsy. The stomach was removed, opened along the greater curve and pinned on card before formalin fixation. Samples of anterior wall including suture lines, posterior wall and lesser curve were processed for paraffin wax embedding and section, and were stained with haematoxylin and eosin. Each section was examined separately for the presence of adenocarcinoma, intestinal metaplasia and dysplasia. This histopathological examination was carried out by a pathologist (N.S.).

The next serial section of each block was stained for NORs. Tissue sections that had previously been fixed in 10 per cent formalin and embedded in paraffin wax were cut into 3-μm thick sections. These were dewaxed in xylene, then rehydrated through ethanol to deionized water. The AgNOR staining solution was prepared as described by Ploton *et al.*[15]. This solution consisted of 2 per cent gelatin in 1 per cent aqueous formic acid added to 50 per cent aqueous silver nitrate in a 1:2 mixture. The staining solution was immediately poured over the slides and the reaction allowed to proceed in the dark for 40 min. AgNOR staining was carried out by a different pathologist (Ö.D.), who examined the sample for histopathological diagnosis and calculated a mean AgNOR score per nucleus. This pathologist found the same histological diagnosis as the first one. AgNOR dots were counted within each nucleus. An oil immersion lens to a maximum magnification of × 1000 was used to count consecutive epithelial cells along glands. Fields were selected at random; 100 cells were examined in each sample. Counts were made in the control group in the superficial foveolar epithelium, in the transitional zone in the metaplasia and dysplasia groups, and in the rats with gastric adenocarcinoma malignant epithelium was counted.

The Kruskal–Wallis test with multiple comparisons was used in the statistical evaluation of data.

Results

The experimentally induced changes of gastric mucosa were mainly located close to the anastomosis. Histopathologically, in the control group no carcinoma, metaplasia or dysplasia was found. In the other group, carcinoma occurred in nine rats (43 per cent), dysplasia in three (14 per cent) and intestinal metaplasia in nine (43 per cent). AgNOR examination showed well defined strongly argyrophilic intranuclear black dots varying in size in all specimens. The lowest mean AgNOR count per nucleus was found in the normal control group, the highest count in carcinoma (*Figures 1* and *2*). A gradual increase in

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carcinogenesis in rats. In the present study the incidence of tumour was 43 per cent, similar to other results.

The AgNOR technique has recently been applied to a number of different tissues and lesions. It has already been shown that the AgNOR count can help distinguish benign and malignant lesions[17,18]. To investigate further AgNORs in human malignant and benign tissue, Mamaev *et al.*[19] used the technique to examine 30 patients with oesophageal and gastric carcinoma. The content of silver granules in the nuclei of tumour cells was significantly higher than in those of normal controls.

In the present study the AgNOR technique in diagnostic gastric pathology was evaluated and applied to normal gastric tissue, gastric cancer, metaplasia and dysplasia. There are some reports on the use of the method in the study of gastric lesions[20,21]. According to these papers it may be possible to differentiate carcinoma from normal tissue with this technique.

There is strong evidence for the pathogenetic sequence of chronic atrophic gastritis, intestinal metaplasia, dysplasia and carcinoma for gastric carcinogenesis[13]. The present results support this sequence of events: the mean number of AgNORs per nucleus increased with higher degrees of cellular atypia. All the values in the tissues showing intestinal metaplasia were $>1{\cdot}6$, which was the highest value found in the normal epithelium. There was no overlap between normal tissue and areas of cellular atypia or malignancy ($P < 0{\cdot}001$).

Although the AgNOR method is not practical for routine use in diagnostic histopathology because it is subjective and time consuming, this study suggests that the technique may help in the evaluation of borderline lesions from normal epithelium rather than in the differentiation of precancerous lesions and carcinoma. Further studies are required to investigate the role of AgNORs as markers of cellular proliferation.

References

1. Stalberg H, Taksdal S. Stomach cancer following gastric surgery for benign conditions. *Lancet* 1971; **ii**: 1175–7.
2. Caygill CPG, Hill MJ, Kirkham JS, Northfield TC. Mortality from gastric cancer following gastric surgery for peptic ulcer. *Lancet* 1986; **i**: 929–31.
3. Clark CG, Fresini A, Gledhill T. Cancer following gastric surgery. *Br J Surg* 1985; **72**: 591–4.
4. Domellof L, Reddy BS, Weisburg JH. Microflora and deconjugation of bile acids in alkaline reflux after partial gastrectomy. *Am J Surg* 1980; **140**: 291–5.
5. Langhans P, Heger RA, Hohenstein J, Bunte H. Gastric stump carcinoma – new aspects deduced from experimental results. *Scand J Gastroenterol Suppl* 1981; **67**: 161–4.
6. Houghton PWJ, Mortensen NJMcC, Thomas WEG, Cooper MJ, Morgan AP, Burton P. Intragastric bile acids and histological changes in gastric mucosa. *Br J Surg* 1986; **73**: 354–6.
7. Mason RC. Duodenogastric reflux in rat gastric carcinoma. *Br J Surg.* 1986; **73**: 801–3.
8. Reed PI, Smith PLR, Haines K, House FR, Walters CL. Gastric juice *N*-nitrosamines in health and gastroduodenal disease. *Lancet* 1981; **ii**: 1037–9.
9. Schlag P, Böckler R, Ulrich H, Peter M, Merkle P, Herfarth Ch. Are nitrite and *N*-nitroso compounds in gastric juice risk factors for carcinoma in the operated stomach? *Lancet* 1980; **i**: 727–9.
10. Siurala M, Varis K, Wiljasalo M. Studies of patients with atrophic gastritis: a 10–15 year follow up. *Scand J Gastroenterol* 1966; **1**: 40–8.
11. Morson BC, Sobin LH, Grundmann E, Johansen A, Nagayo T, Serck-Hanssen A. Precancerous conditions and epithelial dysplasia in the stomach. *J Clin Pathol* 1980; **33**: 711–21.
12. Assad RT, Eastwood GL. Epithelial proliferation in human fundic mucosa after antrectomy and vagotomy. *Gastroenterology* 1980; **79**: 807–11.
13. Correa PA. Human model of gastric carcinogenesis. *Cancer Res* 1988; **48**: 3554–60.
14. Stahl A. The nucleolus and nucleolar chromosomes. In: Jordan EG, Cullins CA, eds. *The Nucleolus.* London: Cambridge University Press, 1982: 1–24.
15. Ploton D, Menager M, Jeannesson P, Himber G, Pigeon F, Adnet JJ. Improvement in the staining and in the visualization of the argyrophilic proteins of the nucleolar organizing regions at the optical level. *Histochem J* 1986; **18**: 5–14.
16. Morgenstern L. Vagotomy, gastroenterostomy and experimental gastric cancer. *Arch Surg* 1968; **96**: 920–3.
17. Crocker J, Skilberg NQ. Nucleolar organizer region associated proteins in cutaneous melanocytic lesions: a quantitative study. *J Clin Pathol* 1987; **40**: 885–9.
18. Smith R, Crocker J. Evaluation of nucleolar organizer regions in breast malignancy. *Histopathology* 1988; **12**: 113–25.
19. Mamaev NN, Mikhailon AA, Irzhanov SI, Bykhoyets IV. Nucleolar organizer activity in epithelial tumor cells of the human colon. *Bulletin of Experimental Biology and Medicine* 1986; **102**: 763–5.
20. Suarez V, Newman J, Hiley C, Crocker J, Collins M. The value of NOR numbers in neoplastic and non-neoplastic epithelium of the stomach. *Histopathology* 1989; **14**: 61–6.
21. Rosa J, Mehta A, Filibe MI. Nucleolar organizer regions in gastric carcinoma and its precursor stages. *Histopathology* 1990; **16**: 265–9.

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Transit disorders of the gastric remnant and Roux limb after Roux-en-Y gastrojejunostomy: relation to symptomatology and vagotomy

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Patients after Roux-en-Y gastrojejunostomy frequently complain of upper abdominal pain, fullness, nausea and vomiting. This study was performed to clarify the relationship of this Roux-en-Y syndrome to transit disorders in the gastric remnant and Roux limb, and to vagal status. Using a questionnaire, 35 of 66 patients operated on between 1976 and 1987 were judged to suffer from the Roux syndrome. Gastrojejunal transit was studied by scintigraphy with a solid test meal in 61 patients, 34 of whom were symptomatic. The median (interquartile range) gastric half-emptying time was longer in symptomatic than in asymptomatic patients (79 (43–146) versus *56 (27–79) min,* $P < 0{\cdot}05$*), and in patients with a bilateral vagotomy than in those without a vagotomy (94 (43–225)* versus *59 (31–77) min,* $P < 0{\cdot}05$*). Stasis in the Roux limb was observed in 18 of 28 symptomatic and in only three of 27 asymptomatic patients (*$P < 0{\cdot}01$*). The median (interquartile range) fraction of activity emptied from the stomach and remaining in the Roux limb at 60 min was 54 (39–60) per cent in symptomatic patients and 33 (21–40) per cent in those without symptoms (*$P < 0{\cdot}01$*). Stasis in the Roux limb was not related to vagal status. No relationship between slow gastric emptying and Roux-limb stasis was found. Slow gastric emptying, Roux-limb stasis or a combination of both was found in 30 of 34 symptomatic and in only nine of 27 asymptomatic patients (*$P < 0{\cdot}01$*). It is concluded that both slow gastric emptying and Roux-limb stasis can be interpreted as causing the Roux syndrome. Vagotomy seems to be the major cause of slow gastric emptying, but it is not related to stasis in the Roux limb.*

Roux-en-Y reconstruction after partial gastrectomy is effective in preventing reflux of biliary and pancreatic juices into the gastric remnant[1–3]. However, it is now recognized that this diversion technique frequently leads to complaints of postprandial pain, epigastric fullness, nausea and vomiting[4–6]. This symptom complex was called by Mathias *et al.* the 'Roux-en-Y syndrome'[7].

Transit disturbances in either the gastric remnant, the jejunal Roux limb or both are assumed to be the main cause of these symptoms. In several studies, delayed emptying of solids from the gastric remnant was found to be associated with the Roux syndrome[7–12]. Some studies have extended the assessment of gastric emptying with transit studies of the Roux limb[8,11–13]. The results of those studies are conflicting with respect to the role of Roux-limb stasis in the pathogenesis of the syndrome. The role of vagotomy in the development of the Roux syndrome also remains unclear[14].

To clarify the relationship between the Roux-en-Y syndrome and transit disorders of the gastric remnant and Roux limb, patients subjected to Roux-en-Y gastrojejunostomy at this institution between 1976 and 1987 were studied. Symptoms were related to gastric emptying and transit through the Roux limb. In addition, the possible contribution of vagotomy and other operative procedures to the development of the syndrome was evaluated.

Patients and methods

Patients

Between 1976 and 1987, Roux-en-Y reconstruction was performed in 82 patients after partial gastrectomy for benign disorders of the stomach or oesophagus.

Sixteen patients did not participate in the study. Ten were excluded for concomitant disease that could affect intestinal motility: four had diabetes mellitus, five had a neurological disorder and one scleroderma. Four patients died from unrelated causes during follow-up and two could not be traced.

There were 46 men and 20 women of mean age 58 (range 20–81) years. Follow-up varied from 2 to 13 (mean 7) years. During follow-up, gastroscopy and/or barium meal examination had been performed in all symptomatic patients to exclude peptic ulcer or anatomical obstruction.

The indications for operation are presented in *Table 1*. In ten of the 66 patients, gastric resection and Roux-en-Y gastrojejunostomy had been performed simultaneously. The other 56 patients had been previously subjected to various numbers of gastric surgical operations (one procedure in 37 patients, two in 13, and three in six). Alkaline reflux gastritis and peptic ulceration were the most common indications for the secondary Roux-en-Y procedures. In ten of these 56 secondary procedures (all Billroth II gastrojejunostomies) the afferent limb was divided and reanastomosed to the more distal jejunum, thereby preserving the previous gastrojejunostomy. In the remaining 46 subjects (five with Billroth I gastroduodenostomy and 41 with Billroth II

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Table 1 *Indications for Roux-en-Y reconstruction*

Indication	Gastrectomy simultaneously with Roux-en-Y procedure ($n = 10$)	Secondary Roux-en-Y procedure ($n = 56$)	Total ($n = 66$)
Alkaline reflux gastritis*	1	26	27
Peptic ulcer*	4	21	25
Persistent reflux oesophagitis	5	6	11
Afferent loop syndrome	0	3	3

*Primary or after partial gastrectomy

gastrojejunostomy) the Roux-en-Y gastrojejunostomy was created after resection of the anastomosis.

The length of the Roux limb varied from 30 to 70 (mean 45) cm. Truncal vagotomy had been carried out in 34 subjects; neural tissue removed at vagotomy was examined histologically in 27. Both vagal trunks were excised in 22 patients, while only one trunk was excised in five. Intraoperative testing for completeness of vagal denervation was not performed.

Eight subjects, all without a vagotomy, developed a jejunal peptic ulcer during follow-up. Four were treated with further resection and vagotomy, the other four with H_2-receptor antagonists.

The study was approved by the hospital medical ethical committee and informed consent obtained from all patients.

Questionnaire

All 66 patients were interviewed using a standard questionnaire, copies of which may be obtained from the author (H.C.J.v.d.M.). This was directed to symptoms, especially to those that may be ascribed to the presence of the Roux-en-Y gastrojejunostomy, i.e. pain, fullness, nausea and vomiting in relation to food intake. The mean duration and frequency of occurrence of each symptom were noted. On the basis of the questionnaire results, patients were classified as symptomatic or asymptomatic. They were considered symptomatic if they fulfilled one or more of the following criteria: pain, fullness and/or nausea with a duration of more than half an hour after the majority of meals; and vomiting more than once a week.

Radionuclide study

Gastrojejunal transit was studied by scintigraphy. After an overnight fast, a ^{99m}Tc-labelled pancake (total energy 1130 kJ: protein 7·5 g, carbohydrate 39 g, fat 9·4 g; radioactivity 10 MBq) was eaten as a test meal[15]. Radioactivity was subsequently measured in a supine position over the whole abdomen using a dual-headed γ camera (Siemens Rota; Siemens Medical, Hoffmann Estates, Illinois, USA) interfaced to a computer (DEC Gamma 11; Digital Equipment, Marlboro, Massachusetts, USA). Digital frames were recorded for 1 h in 1-min periods. After repeatedly viewing the images of all successive frames in film mode, regions of interest were chosen for the stomach, Roux limb and the remainder of the abdomen, using the sum image of all 60 frames. The activity curves for these three regions were obtained by calculating the geometric means of the anterior and posterior curves. The rate of gastric emptying was expressed as the half-emptying time ($t_{1/2}$) and determined by fitting a power exponential curve to the emptying curve of the stomach region[15,16]. The power exponent determines deviations of the emptying curve from a monoexponential decay curve. The emptying curve for solids normally shows a lag phase; with an increasing length of this lag phase, the value of the power exponent will be progressively larger than 1·0. Normal values for $t_{1/2}$ in this institution are 30–90 min for the intact stomach. Slow gastric emptying was defined as $t_{1/2} > 90$ min.

For the assessment of transit through the Roux limb, allowance was made for the filling of the limb (gastric emptying). Calculation of a simple half-emptying time, as previously proposed[13], is highly questionable. Another complicating factor is reflux into the gastric remnant, which frequently occurs. In view of these considerations, Roux-limb stasis was determined by two methods and the results compared. First, the activity curves from the regions of the Roux limb and the rest of the intestine were analysed visually and stasis was defined as an increase of the activity over the region of the Roux limb during the test, accompanied by slow or absent increase of activity over the rest of the intestine (*Figure 1*). Second, the amount of radionuclide activity present in the Roux limb at the end of the test, expressed as a percentage of the amount of activity that had been emptied from the stomach during the test, was determined.

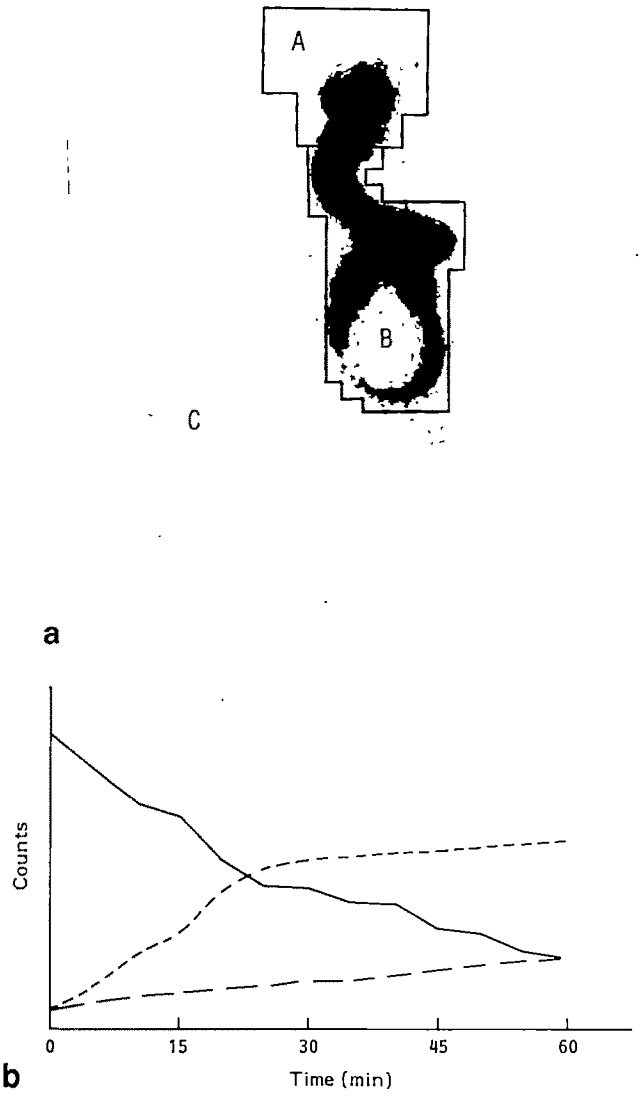

Figure 1 *An example of* a *regions of interest with* b *their activity curves in a scintigraphic study of a patient with normal gastric emptying and stasis in the Roux limb. A, gastric remnant* (——)*; B, Roux limb* (----)*; C, remainder of abdomen* (— —)

Statistical analysis

Wilcoxon's test for paired and unpaired data, Kruskal–Wallis one-way analysis of variance and the χ^2 test were used for statistical analysis[17]. Values are given as median (interquartile range (i.q.r.)). Differences were considered significant at $P < 0.05$.

Results

Questionnaire

Thirty-five patients reported symptoms. Complaints in these 35 were: fullness (31 patients), pain (22), nausea (22) and vomiting (14). All but six patients had more than one symptom. Of the six patients with only one symptom, four had long-lasting fullness with bloating after each meal and two suffered pain after each intake of food. Despite the presence of symptoms, 20 of the 35 patients reported improvement after the Roux-en-Y operation.

No relationship was found between the presence of complaints and the indication for operation, vagal status, the method of creating the Roux-en-Y gastrojejunostomy or the length of the Roux limb.

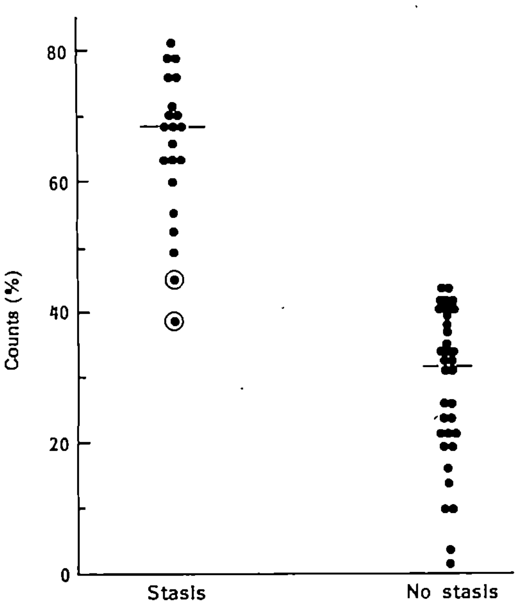

Figure 2 *Counts in the Roux limb at 60 min as a percentage of those emptied from the gastric remnant in 60 min, for 21 patients with Roux-limb stasis and 34 without, as assessed visually.* ⊙, *Patients with a period of reflux from the Roux limb to the gastric remnant just before the 60th minute. Bars are medians*

Table 2 *Transit disorders related to vagal status**

	Bilateral vagotomy ($n = 28$)†	One vagal trunk excised ($n = 5$)	No vagotomy ($n = 28$)
Median (interquartile range) $t_{1/2}$ (min)	94 (43–225)	49 (14–119)	59 (31–77)
No. of patients with Roux-limb stasis	7 of 22‡	2 of 5	12 of 28

$t_{1/2}$, Gastric half-emptying time. *One patient with a vagotomy and four patients without refused to undergo scintigraphy; †21 patients with and seven without histological confirmation; ‡Roux-limb transit could not be evaluated in six patients

Radionuclide studies

Scintigraphy was performed in 61 of the 66 patients; one symptomatic and four asymptomatic patients declined to participate in this part of the study. The $t_{1/2}$ of the gastric remnant ranged from 50 to 300 (median 71) min. The median (i.q.r.) $t_{1/2}$ was 79 (43–146) min in symptomatic and 56 (27–79) min in asymptomatic patients ($P < 0{\cdot}05$). Slow gastric emptying was observed in 16 of the 34 symptomatic and in six of the 27 asymptomatic patients. No significant differences were found for the median (i.q.r.) power exponent between symptomatic and asymptomatic patients (1·16 (0·80–1·78) *versus* 1·26 (1·16–1·80)).

Transit through the Roux limb could not be evaluated reliably in six of the symptomatic patients because of very slow gastric emptying. In the remaining 55 patients undergoing scintigraphy, stasis in the Roux limb, as determined by visual analysis, was observed in 18 of the 28 symptomatic and in only three of the 27 asymptomatic patients ($P < 0{\cdot}01$). The median (i.q.r.) activity in the Roux limb at the end of the test, expressed as the fraction of activity emptied from the gastric remnant during the test, was higher in symptomatic than in asymptomatic patients (54 (39–60) *versus* 33 (21–40) per cent, $P < 0{\cdot}01$). Good agreement was found between the two methods for determination of Roux-limb stasis (*Figure 2*).

The simultaneous presence of both slow gastric emptying and Roux-limb stasis was observed in four symptomatic and in no asymptomatic patients. Thus, 30 of 34 symptomatic patients had either slow gastric emptying, stasis in the Roux limb or both, whereas only nine of 27 asymptomatic patients had one or more of these transit disorders ($P < 0{\cdot}01$). Two of the four symptomatic patients without slow transit through either stomach or Roux limb had fast emptying of the gastric remnant ($t_{1/2} < 30$ min); in one this was accompanied by symptoms of dumping. No explanation was found for the symptoms in the other two patients.

The presence of stasis in the Roux limb did not appear to be associated with a reduced gastric emptying rate, since gastric emptying times in patients with such stasis were similar to those in patients without. The median (i.q.r.) $t_{1/2}$ was 60 (41–80) min in the presence (21 patients) and 58 (27–110) min in the absence (34 patients) of Roux-limb stasis.

In evaluating the effect of vagotomy and other operative procedures on transit, a statistically significant difference ($P < 0{\cdot}05$) in $t_{1/2}$ was found between patients with a bilateral vagotomy and those without vagotomy (*Table 2*). No significant difference was found for the median (i.q.r.) power exponent between these two groups (1·23 (0·90–1·81) *versus* 1·24 (0·80–1·88)). No relationship was found between stasis in the Roux limb and vagotomy (*Table 2*). The method of creating the Roux-en-Y gastrojejunostomy in the secondary procedures, the number of previous gastric operations (*Table 3*) and the indication for operation (*Table 4*) had no effect on transit through the gastric remnant or Roux limb. Transit disorders through either the Roux limb or gastric remnant were not correlated with the length of the Roux limb. The mean(s.d.) length of the Roux limb in patients with stasis was 47(8) cm, compared with 44(6) cm in those without stasis (P not significant). Mean(s.d.) Roux-limb length was 44(7) and 45(7) cm for patients with and without slow gastric emptying respectively.

Table 3 *Transit disorders related to the number of previous gastric operations*

No. of previous gastric operations	No. of patients*	Median (interquartile range) $t_{1/2}$ (min)	No. of patients with Roux-limb stasis
0	8	75 (49–83)	2 of 8
1	36	64 (26–139)	12 of 31†
≥2	17	79 (57–114)	7 of 16‡

$t_{1/2}$, Gastric half-emptying time. *Scintigraphy was refused by two patients without previous gastric surgery, one patient with one and two with two previous gastric operations; †Roux-limb transit could not be evaluated in five patients; ‡Roux-limb transit could not be evaluated in one patient

Table 4 *Transit disorders related to the indication for the Roux-en-Y procedure*

Indication	No. of patients*	Median (interquartile range) $t_{1/2}$ (min)	No. of patients with Roux-limb stasis†
Alkaline reflux gastritis‡	26	59 (34–129)	9 of 24
Peptic ulcer‡	21	79 (40–131)	8 of 17
Persistent reflux oesophagitis	11	71 (27–86)	2 of 11
Afferent loop syndrome	3	65 (59–116)	2 of 3

$t_{1/2}$, Gastric half-emptying time. *Scintigraphy was refused by one patient with alkaline reflux gastritis and four with peptic ulcer; †Roux-limb transit could not be evaluated in two patients with alkaline reflux and in four with peptic ulcer; ‡primary or after partial gastrectomy

Discussion

The present study is the first to report both emptying of the gastric remnant and transit through the Roux limb in relation to symptoms and vagotomy in a large group of patients. Since only a few patients did not participate, the results can be assumed to be representative for the whole group.

Four studies on transit through the Roux limb have so far been reported[8,11–13], but in none of these was Roux-limb stasis clearly defined. In determining transit through the limb by scintigraphy one is faced with two main problems: identification of the Roux limb and the definition and quantification of stasis. By repeatedly reviewing all images sequentially in film mode the Roux limb was identified in most patients in the present study without problems, except in six with very slow gastric emptying. Two different methods were used to assess Roux-limb stasis. With both of these the filling as well as the emptying of the limb was taken into account. Although one method was based on visual analysis of the activity curves, and the other on the calculation of retained activity in the Roux limb, close agreement between the two methods was found.

The high proportion of patients in this study having symptoms consistent with the Roux-en-Y syndrome is in accordance with results of others[4–6,18]. In spite of these complaints, most subjects felt themselves to have improved after the Roux-en-Y procedure; the reliability of this finding is, however, questionable in view of the retrospective nature of this part of the study, with a mean follow-up of 7 years.

The results of this study provide strong evidence that the Roux syndrome is caused by transit disorders of the gastric remnant and/or Roux limb. In symptomatic patients the mean gastric half-emptying time was significantly longer than in those without symptoms. Similar results have also been described in patients after partial gastrectomy and Billroth II anastomosis[19]. Ritchie[20] reported that slow gastric emptying after partial gastrectomy and Roux-en-Y reconstruction normalized during longer follow-up; this was not confirmed in the present study as the mean follow-up was 7 (minimum 2) years.

So far the cause of the slow emptying of the gastric remnant after Roux-en-Y gastrojejunostomy has not been clarified. This study did not verify the hypothesis[7] that slowing of gastric emptying is caused by motility disorders in the Roux limb leading to a functional obstruction: in the patients in whom both gastric emptying and transit through the Roux limb could be evaluated, stasis in the latter was not attended by slower gastric emptying. More likely, slow emptying of the gastric remnant is the result of gastroparesis resulting from vagal denervation: gastric emptying was significantly slower in patients who had undergone complete vagotomy. This is in accordance with the studies of Stadaas and Aune[21], and of Azpiroz and Malagelada[22], who found that the stomach could not maintain intragastric pressure after truncal vagotomy.

The consequences of vagotomy with respect to the emergence of gastroparesis raise the issue of whether or not to add vagotomy in patients in whom Roux-en-Y gastrojejunostomy is performed. The reason for doing so is the observed high risk of recurrent peptic ulcer after Roux-en-Y gastrojejunostomy, because of the absence of neutralizing duodenal contents near the gastrojejunal anastomosis[23]. The results of the present study, in which 25 per cent of patients in the group without vagotomy had peptic ulcers, compared with none in the group with vagotomy, support this. Although it thus seems wise to add vagotomy to the Roux-en-Y procedure to prevent peptic ulceration, this may result in incapacitating gastroparesis, whereas recurrent ulceration can now almost always be treated medically.

The present study shows that, in addition to slow gastric emptying, stasis in the Roux limb plays an important role in the emergence of symptoms after Roux-en-Y gastrojejunostomy. This is further supported by a recent study on treatment of the Roux syndrome with cisapride[24], in which it was found that acceleration of Roux-limb transit was independently associated with symptomatic improvement. Motility disturbances in the Roux limb are most probably the cause of these transit disorders, because anatomical obstruction was excluded in all the present patients. Moreover, manometric studies have shown major motor abnormalities in the Roux limb in many such patients[7,11,25]. It seems most likely that these disorders in the Roux limb are the consequence of disconnection of the limb from the duodenum, leaving this part of the jejunum no longer under appropriate electrical control of the duodenal pacemaker[26,27]. The role of vagotomy in the pathogenesis of motility disorders in the Roux limb is questionable. In contrast to the experimental work of Vogel *et al.*[28], no relationship between transit disorders in the Roux limb and vagal denervation was found. Previous studies have suggested a relationship between development of the syndrome and the length of the Roux limb[4], the number of previous gastric operations[5,12] and the indication for surgery[5]. These findings were not confirmed in the present study.

In conclusion, the results of this study show that: (1) both slow emptying of the gastric remnant and Roux-limb stasis are frequently found after partial gastrectomy and Roux-en-Y reconstruction; (2) both are clearly related to symptoms and can be assumed to be the main cause of the so-called Roux-en-Y syndrome; (3) vagotomy is the major cause of slow emptying of the gastric remnant, but is not related to stasis in the Roux limb; and (4) other factors such as the indication for operation, number of previous gastric operations and length of the Roux limb are not involved in the aetiology of the Roux syndrome.

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References

1. Fiore AC, Malangoni MA, Broadi TA, Madura JA, Jesseph JE. Surgical management of alkaline reflux gastritis. *Arch Surg* 1982; **117**: 689–4.
2. De Langen ZJ, Slooff MJH, Jansen W. The surgical treatment of postgastrectomy reflux gastritis. *Surg Gynecol Obstet* 1984; **158**: 322–6.
3. Malagelada J-R, Phillips SF, Shorter RG *et al.* Postoperative reflux gastritis: pathophysiology and long-term outcome after Roux-en-Y diversion. *Ann Intern Med* 1985; **103**: 178–83.
4. Gustavsson S, Ilstrup DM, Morrison P, Kelly KA. Roux-Y stasis syndrome after gastrectomy. *Am J Surg* 1988; **155**: 490–4.
5. Britton JP, Johnston D, Ward DC, Axon ATR, Barker MCH. Gastric emptying and clinical outcome after Roux-en-Y diversion. *Br J Surg* 1987; **74**: 900–4.
6. Ferguson GH, MacLennon I, Taylor TV, Torrance HB. Outcome of revisional gastric surgery using a Roux-en-Y biliary diversion. *Br J Surg* 1990; **77**: 551–4.
7. Mathias JR, Fernandez A, Sninsky CA, Clench MH, Davis RH. Nausea, vomiting and abdominal pain after Roux-en-Y anastomosis: motility of the jejunal limb. *Gastroenterology* 1985; **88**: 101–7.
8. Hinder RA, Esser J, DeMeester TR. Management of gastric emptying disorders following the Roux-en-Y procedure. *Surgery* 1988; **104**: 765–72.
9. Vogel SB, Woodward ER. The surgical treatment of chronic gastric atony following Roux-Y diversion for alkaline reflux gastritis. *Ann Surg* 1989; **209**: 756–63.
10. Eckhauser FE, Knol JA, Raper SA, Guice KS. Completion gastrectomy for postsurgical gastroparesis syndrome. *Ann Surg* 1988; **208**: 345–53.
11. Pellegrini CA, Patti MG, Lewin M, Way LW. Alkaline reflux gastritis and the effect of biliary diversion on gastric emptying of solid food. *Am J Surg* 1985; **150**: 166–71.
12. Ferguson GH, Rose M, MacLennan I, Taylor TV, Torrance HB. Vomiting after Roux-en-Y biliary diversion: relationship to surgical technique. *Br J Surg* 1990; **77**: 548–50.
13. Perino LE, Adcock KA, Goff JS. Gastrointestinal symptoms, motility and transit after the Roux-en-Y operation. *Am J Gastroenterol* 1988; **83**: 380–5.
14. van der Mijle HCJ, Kleibeuker JH, Bleichrodt RP, Limburg AJ, Hesselink EJ. Gastric and jejunal motility disturbances after

Roux-en-Y gastrojejunostomy. *Scand J Gastroenterol Suppl* 1989; **24**: 69–74.

15. Kleibeuker JH, Beekhuis H, Piers DA, Schaffalalitzky de Muckadell OB. Retardation of gastric emptying of solid food by secretin. *Gastroenterology* 1988; **94**: 122–6.
16. Elashoff JD, Reedy TJ, Meyer JH. Analysis of gastric emptying data. *Gastroenterology* 1982; **83**: 1306–12.
17. Siegel S, Castellani NJ. *Non-parametric Statistics*. 2nd ed. New York: McGraw Hill, 1988.
18. Boren CH, Way LW. Alkaline reflux gastritis: a reevaluation. *Am J Surg* 1980; **140**: 40–6.
19. Smout AJPM, Akkermans LMA, Roelofs JMM, Pasma FG, Oei HY, Wittebol P. Gastric emptying and postprandial symptoms after BII resection. *Surgery* 1987; **101**: 27–34.
20. Ritchie WP. Alkaline reflux gastritis. Late results on a controlled trial of diagnosis and treatment. *Ann Surg* 1986; **203**: 537–44.
21. Stadaas J, Aune S. Intragastric pressure/volume relationship before and after vagotomy. *Acta Chirurgica Scandinavica* 1970; **136**: 611–15.
22. Azpiroz F, Malagelada J-R. Gastric tone measured by an electronic barostat in health and post-surgical gastroparesis. *Gastroenterology* 1987; **92**: 934–43.
23. Rieu PNMA. *Gastrectomy with Roux-en-Y Anastomosis for Peptic Ulcer*. Doctoral thesis. Nijmegen, Netherlands: Jansen/Print, 1989.
24. van der Mijle HCJ, Beekhuis H, Bleichrodt RP, Kleibeuker JH. Cisapride in treatment of Roux-en-Y syndrome. *Dig Dis Sci* 1991; **36**: 1691–6.
25. van der Mijle HCJ, Limburg AJ, Beekhuis H, Bleichrodt RP, Kleibeuker JH. Motility disturbances of the Roux-limb after Roux-en-Y gastrojejunostomy. *Gastroenterology* 1990; **98**: A399.
26. Vantrappen G, Coremans G, Janssens J, Mantides A, Vanden Borre F. Inversion of the slow-wave frequency gradient in symptomatic patients with Roux-en-Y anastomoses. *Gastroenterology* 1991; **101**: 1282–8.
27. Karlstrom LH, Soper NJ, Kelly KA, Phillips SF. Ectopic jejunal pacemakers and enterogastric reflux after Roux gastrectomy: effect of intestinal pacing. *Surgery* 1989; **106**: 486–95.
28. Vogel SB, Vair DB, Woodward ER. Alterations in gastric emptying of ^{99m}technetium labeled solids following sequential antrectomy, truncal vagotomy and Roux-Y gastroenterostomy. *Ann Surg* 1983; **198**: 506–15.

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Omental patching of a large perforated duodenal ulcer: a new method

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The commonest perforation of the upper gastrointestinal tract is a duodenal ulcer. In 1929 Cellan-Jones described the most widely used technique for dealing with perforated ulcers, in which a strand of omentum is drawn under an arch of full-thickness sutures placed on either side of the perforation[1,2]. Although the omental patch technique is useful for small holes, it is associated with releakage when the perforation is large[2]. In this unit such a method of patching a large ulcer has occasionally been associated with releakage within 48 h. This prompted a consideration of an alternative technique for patching a large perforated duodenal ulcer.

Surgical technique

A nasogastric tube is advanced by the anaesthetist and guided into the duodenum by the operating surgeon. The end of the tube is directed to protrude through the perforated ulcer into the peritoneal cavity. A piece of omentum is attached to the tube using a no. 1 chromic catgut tie. The tube is then withdrawn and the plug pulled into the perforation, thus blocking the latter securely rather than merely patching the surface (*Figure 1*). The edges of the omental plug are tacked to the margins of the ulcer using one or two catgut sutures. Meticulous peritoneal toilet is performed and the subhepatic space drained with a fine suction drain. The nasogastric tube is placed on low-pressure suction (50 mmHg) for 72 h and the patient is given a H_2-receptor antagonist intravenously. The nasogastric tube is removed after 1 week, during which time the catgut suture attaching it to the omentum has dissolved away.

Results

This technique was used to patch large anterior perforated duodenal ulcers in three consecutive patients with perforations >1 cm in diameter. The postoperative courses were uncomplicated by any further leakage and all three were discharged within 8 days. Endoscopy 6 weeks later showed a healed duodenum in all three patients, with a tiny anterior scar.

Discussion

There are several conventional options for dealing with a perforated duodenal ulcer at laparotomy. The first is simple closure[2,3], a method that can be used only for small perforations. Direct apposition is often not possible because of the induration of oedema, and the sutures may cut through the inflamed duodenal wall.

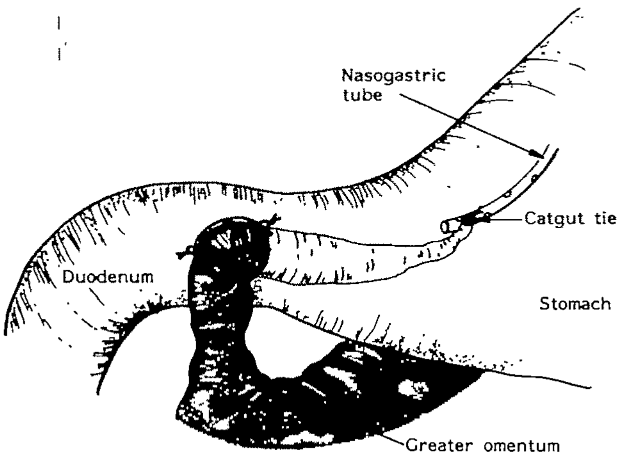

Figure 1 *The nasogastric tube has been passed out through the perforation into the peritoneal cavity where a piece of omentum has been attached to it with a catgut tie. The tube is then withdrawn into the stomach, pulling the omental plug into the perforation*

The second option of closure with an omental patch is the most widely used technique[1–3]. The method described by Cellan-Jones[1] may be unreliable for oversewing ulcers >5 mm in diameter. The major disadvantage of this method is that the omental plug is rendered ischaemic by tying three sutures across it to hold it over the hole. Such ischaemia may give rise to necrosis with subsequent releakage.

The third option is the use of a definitive procedure. The decision to use such an operation should be based on associated risk factors for the individual patient[4]. Serious medical illness, preoperative shock, and longstanding perforation (>24 h) greatly increase mortality. When all three of these risk factors were present all patients died, and 46 per cent with two risk factors did so[4]. Thus, if any risk factor is present, simple closure is advised.

The method of omental patching described avoids the development of omental ischaemia. In the critically ill patient with a large perforated duodenal ulcer who is deemed unsuitable for partial gastrectomy, we believe this to be a safe method of achieving a firm seal.

References

1. Cellan-Jones CJ. A rapid method of treatment in perforated duodenal ulcer. *BMJ* 1929; i: 1076–7.
2. Hugh TB. Perforated peptic ulcers. In: Schwarz S, Ellis HA, eds. *Maingot's Abdominal Operations*. 9th ed. Connecticut: Appleton and Lange, 1990: 627–45.
3. Sawyers JL. Acute perforation of peptic ulcer. In: Scott HW, Sawyers JL, eds. *Surgery of the Stomach, Duodenum and Small Intestine*. 2nd ed. Boston: Blackwell Scientific, 1992: 566–72.
4. Boey J, Choi S, Algaratman TT *et al.* Risk stratification in perforated peptic duodenal ulcers: a prospective validation of predictive factors. *Am J Surg* 1987; **205**: 22–6.

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Bacterial translocation in acute liver failure induced by 90 per cent hepatectomy in the rat

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Bacterial infection and bacteraemia have been observed in patients with acute liver failure. The exact source of bacteria and nature of pathophysiological mechanisms explaining the development of infection remain unclear. In the present study, acute liver failure was induced by 90 per cent hepatectomy in the rat. The mesenteric lymph nodes and organs were harvested aseptically for bacteriological culture after sham operation or 90 per cent hepatectomy. Function of the liver and reticuloendothelial system (RES) was assayed; gut oxygen extraction was also measured. Translocation of enteric bacteria occurred 2 h after operation and increased with time following hepatectomy. Overgrowth of Escherichia coli *in the distal small intestine started 2 h after operation. RES function decreased immediately after 90 per cent hepatectomy; uptake rates per gram tissue in other organs increased significantly. These results indicate that bacterial translocation occurred early after 90 per cent hepatectomy, associated with a decrease in RES function and gut oxygen extraction, and overgrowth of intestinal bacteria.*

Bacteraemia and bacterial infection are frequently seen in association with acute liver failure, occurring in 20–50 per cent of patients[1,2]. Rolando *et al.*[3] recently reported that, of 50 patients with acute liver failure, defined as the development of hepatic encephalopathy, 40 had bacteriologically proven infection. The liver constitutes the major part of the reticuloendothelial system (RES) function, with a role in eliminating bacteria from the blood[4–6]. Thus, the high incidence of bacterial infection in acute liver failure could be explained by impaired RES function[7], together with defective serum opsonization and complement deficiency[8]. However, the exact pathophysiological mechanisms underlying the bacteraemia and bacterial infection in acute liver failure remain unclear.

Since Berg and Garlington[9] defined the concept of bacterial translocation, many studies of sepsis of gut origin have been carried out in models of haemorrhagic shock[10,11], thermal injury[12,13], total parenteral nutrition[14] and malnutrition[15]. The escape of bacteria from the gastrointestinal tract into the bloodstream and various organs has been proposed to be due to influence on the intestinal barrier, immunological functions and microcirculation of the intestinal wall[16]. Bacterial translocation from the alimentary tract in rats with haemorrhagic shock has been emphasized[17]. In the early 1980s, Berg[18] suggested that translocation of endogenous bacteria from the gastrointestinal tract occurred as a subacute or chronic process occurring over several days. Koziol *et al.*[11] recently reported that translocation of enteric bacteria occurred within 2 to 4 h in the acute phase of haemorrhagic shock.

The gut might act as a site of entry for bacteria in acute liver failure. The present study examined the incidence of bacterial translocation in rats with liver failure induced by 90 per cent hepatectomy. Bacteriological blood and tissue cultures, and RES function were studied to explore the source of bacteraemia and infection in acute liver failure and the relationship between bacterial translocation and RES activity.

Materials and methods

Adult male Sprague–Dawley rats (Anticimex, Stockholm, Sweden) weighing 250–300 g were used. The animals were fed standard rat chow (R_3; Astra-Ewos, Södertälje, Sweden) and water was freely available. The rats were acclimatized to laboratory conditions for 4–6 days; they were subjected to a diurnal cycle of 12 h day and night and kept in mesh stainless steel cages (three rats per cage) individually maintained at constant temperature (22°C).

Hepatectomy of 90 per cent in the rat has been shown to result in acute liver failure[19,20]. Under light ether anaesthesia and aseptic conditions, a laparotomy was performed including removal of the xiphoid. The liver was freed from the surrounding ligaments. The 90 per cent hepatectomy performed was a modification of that described previously[19]. The left, median, right upper and lower lobes or the major part of the right lower lobe were in general included in the hepatectomy, leaving only the caudate or sometimes also parts of the right lower lobe. After resection, a coagulant (Spongostan; Ferrosan, Copenhagen, Denmark) was used to stop bleeding on the cut surfaces. Subtotal hepatectomy of 90 per cent was defined by weight, related to the total liver weight, estimated before the operation as 4·5 per cent of body-weight[20]. Sham operation was carried out by laparotomy with removal of the xiphoid and separation of the liver without resection.

Using a sterile technique, 0·2 ml blood was taken from the tail vein immediately before operation and at 1, 2, 4 and 6 h afterwards for bacterial culture. At the same time as blood sampling, 0·2 ml autologous blood was injected. Rats undergoing 90 per cent hepatectomy were killed by anaesthetic overdose 1, 2, 4 or 6 h after hepatectomy. A midline incision was made through the skin and muscular layers of the abdomen. After sterilizing the outside of the parietal peritoneum with 70 per cent alcohol, the mesenteric lymph nodes (MLNs), liver, kidneys and spleen were harvested for bacterial culture as previously described[21]. Using the same method, the thoracic cavity was entered and part of the lungs sampled for bacterial culture. Bacterial contamination of the operative field and exposed viscera were determined as described by Deitch *et al.*[12]. Parts of the MLNs, spleen, liver, kidneys and lungs were weighed before culture. Parts of the proximal jejunum (5–7 cm from the ligament of Treitz), distal ileum (10–12 cm from the caecum) and transverse colon were removed for bacterial culture and weighed. Blood samples were immediately inoculated in 3 ml blood culture medium. The medium used for aerobic bacteria included 30 g Tryptone Soya Broth (Difco Laboratories, Detroit, Michigan, USA), 1 g $Na_2HPO_4 \cdot 2H_2O$, 0·25 g sodium polyanetholsulphonate, 7·5 g glucose and 10 g sucrose per litre. Anaerobic bacteria were grown in 35 g Columbia broth, 0·5 g

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$Na_2HPO_4 \cdot 2H_2O$, 0·25 g sodium polyanetholsulphonate, 7·5 g glucose and 0·12 g cysteinhydrochloride again dissolved in distilled water to 1 litre. The harvested organs were placed in test tubes containing 3 ml Brain Heart Infusion Broth (Difco) and homogenized for culture of aerobic, microaerophilic and anaerobic bacteria. The intestinal suspension was mixed in a Super Mixer (Lab-Line Instruments, Meprose, New York, USA) and allowed to settle. The supernatant (0·2 ml) was used as inoculum for the culture. Blood agar plates consisting of Blood Agar Base (Oxoid, Basingstoke, UK) supplemented with 4 per cent horse blood were used to count viable bacteria. In some series of experiments for viable count determinations of *Escherichia coli*, McConkey agar (Oxoid) was also used. All media used for aerobic culture of organ or blood samples were incubated at 37°C for at least 3 days, while the anaerobic organ samples were cultured at 37°C for 7 days before being regarded as negative. Enteric Gram-negative bacteria were identified by the API 20 system (BioMerieux, Marcy-l'Etoile, France) and *Lactobacillus acidophilus* by API 50 CH (Analytab Products, Plainview, New York, USA). All other aerobic, microaerophilic and anaerobic microbes isolated were identified by standard procedures[22,23]. The numbers of living bacteria were calculated and expressed as number of living organisms per gram tissue.

E. coli (serotype 046:KI:H31) were cultured overnight in Todd–Hewitt broth, heat-killed at 80°C for 10 min, washed three times in phosphate-buffered saline (PBS) (Sigma Chemicals, St Louis, Missouri, USA) including 0·03 mol/l phosphate and 0·12 mol/l saline and at pH 7·2, and then suspended in PBS. Bacterial radiolabelling with ^{125}I was performed with the protein-labelling method described by McConahey and Dixon[24] using chloramine T as the oxidizing agent. This radiolabelling was followed by three additional washings in PBS and centrifugations (1800 r.p.m. for 10 min) after which the suspension was frozen at −20°C and thawed immediately before use. The radioactivity was approximately 3×10^7 c.p.m. per ml bacterial suspension.

The phagocytic index was used to assay RES function by the blood clearance rate of ^{125}I-radiolabelled *E. coli*. Radiolabelled bacteria (0·1 ml) at a dose of 3×10^6 c.p.m. per rat were injected through a femoral vein catheter (outer diameter 0·94 mm; Dow Corning, Michigan, USA) and 150 μl blood sampled immediately before and 2, 5, 8, 10 and 15 min after bacterial injection through a femoral artery catheter (outer diameter 0·75 mm; Portex, Hythe, UK). The phagocytic index was measured by a slight modification of the method of Braude *et al.*[25]. Estimation of the uptake rate of ^{125}I-radiolabelled *E. coli* was performed according to a modification of the principle described by Arii *et al.*[26]. The uptake rate of radiolabelled bacteria per gram tissue in the liver, spleen, lungs and kidneys was determined when the animals were killed 15 min after intravenous injection of ^{125}I-radiolabelled *E. coli*; this was expressed as the uptake ability per gram tissue. The uptake rate is equal to the ratio of radioactivity per gram tissue to radioactivity in the blood 15 min before organ harvest, multiplied by 100. The uptake percentage distribution of radiolabelled bacteria in each organ was used to express its RES function, defined as the uptake in each organ as a proportion to the total uptake in all four major organs immediately, 2 and 6 h after 90 per cent hepatectomy.

To measure oxygen extraction, 0·3 ml blood was taken from the abdominal aorta, inferior vena cava and portal vein before death. Determination of haemoglobin and blood gas analysis were performed using a Haemoglobin Analyzer (Vitratron HBF 200, Amsterdam, The Netherlands) and Acid–Base Analyzer (ABL 30; Radiometer, Copenhagen, Denmark). Oxygen content in the arterial, systemic and portal venous blood was calculated according to Salloum *et al.*[27]. Whole-body oxygen extraction was determined from the difference in oxygen content of the abdominal aorta (A) and oxygen content of the inferior vena cava (SV):

$$\text{Body oxygen extraction} = (A - SV)/A$$

Oxygen extraction in the gastrointestinal tract was assayed by the difference between A and oxygen content of the portal vein (PV):

$$\text{Gut oxygen extraction} = (A - PV)/A$$

The femoral artery was aseptically cannulated (outer diameter 0·75 mm; Portex). The mean arterial pressure was measured using a Mingograf (Siemens–Elema, Erlangen, Germany) before the operation and immediately, 1, 2, 4 and 6 h afterwards.

A volume of 0·5 ml blood was taken from the tail vein after 90 per cent hepatectomy or sham operation in animals not challenged with ^{125}I-radiolabelled bacteria to measure the plasma levels of aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), alkaline phosphatase and bilirubin the day before and immediately, 1, 2, 4 and 6 h after operation. After blood sampling, 0·5 ml sterile saline was injected into the tail vein.

At 3 days before operation 1 ml blood was taken from all experimental animals for autologous blood transfusion during operation and during blood sampling to keep arterial pressure above 90 mmHg.

The study included the following four experiments. In controls ($n = 6$), a laparotomy was carried out and the liver mobilized, followed by bleeding to achieve arterial pressure of 90 mmHg. Rats with 90 per cent subtotal hepatectomy were randomized to studies on bacterial translocation ($n = 28$), RES function ($n = 24$) or liver function ($n = 24$). Finally, another 24 rats were used to assay body and gut oxygen extraction. Six or ten rats were studied at each time point. Standardized portions of each organ were taken for the determination of RES function: these were the caudate lobe of the liver, the middle of the spleen, the middle of the kidney and the lower right lobe of the lungs. In this study animals measured did not include those which had died before planned termination of the experiment.

Student's t test and χ^2 analysis were used for statistical comparisons.

Results

The operating time for all surgical procedures including sham operation and 90 per cent hepatectomy did not exceed 10 min. The preoperative mean(s.e.m.) arterial pressure was 110(12) mmHg, decreasing to 80(5) mmHg after hepatectomy. Clinical signs of liver failure were noted from 2 to 4 h after operation, including trembling, somnolence, lethargy or even coma. Liver function tests gave further evidence of acute hepatic failure induced by 90 per cent hepatectomy. Enzyme and bilirubin levels increased after 1 h and were significantly raised 2–4 h after liver resection ($P < 0·05$) (*Table 1*), increasing with time after hepatectomy (at 6 h, $P < 0·01$). The mortality rates were 10 and 30 per cent at 4 and 6 h respectively after 90 per cent hepatectomy; no animal died within 2 h of the procedure.

Blood cultures in controls and 1 h after hepatectomy were negative. In contrast, 80 per cent of blood cultures in rats undergoing hepatectomy were positive for bacterial growth 2 h after operation and 100 per cent were positive 4 h after (*Table 2*), significantly different from both controls and cultures 1 h after liver resection ($P < 0·01$). The incidence of positive

Table 1 *Mean(s.e.m.) plasma levels of liver enzymes and bilirubin at different times after 90 per cent hepatectomy in the rat*

	ALAT (μkat/l)	ASAT (μkat/l)	Alkaline phosphatase (μkat/l)	Bilirubin (μmol/l)
Control (sham operation)	3·5(0·8)	6·3(0·5)	8·4(0·6)	8·2(0·7)
Time after operation (h)				
0	5·7(1·0)	8·6(0·8)	10·3(0·9)	11·9(0·5)
1	6·4(0·8)	8·8(1·2)	12·6(0·8)	14·1(0·6)
2	7·4(1·1)*	10·7(1·5)*	15·2(1·0)*	15·6(3·2)*
4	8·3(1·4)*	13·3(0·9)*	16·4(2·0)*	17·7(3·2)*
6	11·2(2·2)†	15·5(2·4)†	18·1(3·4)†	20·4(3·7)†

Each group contained 12 rats. ALAT, alanine aminotransferase; ASAT, aspartate aminotransferase. *$P < 0·05$; †$P < 0·01$ (*versus* control, Student's t test)

Table 2 *Incidence of positive cultures in blood and organs at different times after 90 per cent hepatectomy in the rat*

	No.	Blood	MLNs	Liver	Spleen	Lungs	Kidneys
Control (sham operation)	6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Time after operation (h)							
1	6	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
2	10	8 (80)†	8 (80)†	5 (50)	5 (50)	1 (10)	1 (10)
4	6	6 (100)†	6 (100)†	4 (67)	5 (83)*	3 (50)	2 (33)
6	6	6 (100)†	6 (100)†	6 (100)	5 (83)*	6 (100)	3 (50)

Values in parentheses are percentages. MLNs, mesenteric lymph nodes. *$P < 0{\cdot}05$ (*versus* control); †$P < 0{\cdot}01$ (*versus* control); χ^2 test

Table 3 *Mean(s.e.m.) content of* Escherichia coli *in blood and organs at different times after 90 per cent hepatectomy in the rat*

Time after operation (h)	Blood (c.f.u. × 10^3/ml)	MLNs (c.f.u. × 10^3/g)	Liver (c.f.u. × 10^2/g)	Spleen (c.f.u. × 10^2/g)	Lungs (c.f.u. × 10^2/g)
2	2·4(1·2)	5·6(0·6)	0·7(0·1)	1·8(0·2)	2·2 ($n = 1$)
4	22·1(7·6)†	17·8(1·5)†	1·4(0·2)*	5·7(1·0)*	7·4(0·7)
6	7·9(2·2)§	33·5(5·5)†§	1·6(0·1)†	34·7(2·3)†§	13·0(2·8)‡

c.f.u., Colony-forming units; MLNs, mesenteric lymph nodes. *$P < 0{\cdot}05$ (*versus* 2 h after operation); †$P < 0{\cdot}01$ (*versus* 2 h after operation); ‡$P < 0{\cdot}05$ (*versus* 4 h after operation); §$P < 0{\cdot}01$ (*versus* 4 h after operation); Student's *t* test

Table 4 *Mean(s.e.m.) content of* Escherichia coli *in the distal small intestine and colon in rats at different times after 90 per cent hepatectomy*

Time after operation (h)	Distal small intestine (c.f.u. × 10^4/g)			Colon (c.f.u. × 10^5/g)		
	Hepatectomy	Control	*P**	Hepatectomy	Control	*P**
2	5·7(2·1)	0·9(0·4)	0·023	3·3(9·8)	0·7(0·2)	0·021
4	5·1(0·9)	0·9(0·4)	0·002	27·7(8·5)	n.d.	0·01†
6	n.d.	n.d.	—	92·6(31·0)	n.d.	0·014†

Each group contained six rats. c.f.u., Colony-forming units; n.d., not determined. *Student's *t* test (†*versus* control at 2 h)

bacterial cultures in the MLNs, liver, spleen and lungs is shown in *Table 2*. Bacterial growth in the MLNs and spleen occurred 2 h after 90 per cent hepatectomy, while cultures were negative in controls and 1 h after hepatectomy. The number of viable organisms in the MLNs and the various organs gradually increased with time following hepatectomy. *E. coli* dominated among isolated bacteria, although enterococci, streptococci, *Klebsiella* and *Proteus mirabilis* were also demonstrated. Quantitative cultures of *E. coli* isolated from blood and organ cultures in rats subjected to hepatectomy are shown in *Table 3*. The number of *E. coli* in blood cultures 4 h after hepatectomy significantly increased compared with 2 h after operation ($P < 0{\cdot}01$) while no significant difference was seen at 2 h compared with 6 h after operation. The number of bacteria in the MLNs gradually increased with time after 90 per cent hepatectomy. In the liver, spleen and lungs the number of *E. coli* significantly increased after 4 and 6 h ($P < 0{\cdot}05$). No growth of *E. coli* in the proximal intestine was demonstrated. The number of *E. coli* cultured in both the distal small intestine and colon in rats subjected to 90 per cent hepatectomy was significantly higher than in controls from 2 h after operation ($P < 0{\cdot}05$) (*Table 4*). The number of *E. coli* in the distal small intestine 4 h after hepatectomy was not different from that in the colon in controls ($P = 0{\cdot}57$).

The phagocytic index comparing the time intervals 2–5, 6–8, 9–10 and 11–15 min after intravenous challenge with ^{125}I-radiolabelled bacteria is shown in *Figure 1*. During the initial phase (2–5 min), the uptake ability of the rats receiving hepatectomy was markedly impaired ($P < 0{\cdot}001$). Phagocytic index at the various times after 90 per cent hepatectomy did not differ.

The uptake rate of ^{125}I-radiolabelled *E. coli* per gram organ tissue and the percentage distribution of uptake in the four organs after hepatectomy is shown in *Table 5*. Although the uptake rate in the liver remnant started to increase 2 h after hepatectomy and was significantly increased 6 h after ($P < 0{\cdot}05$), total uptake ability of the liver diminished immediately following 90 per cent hepatectomy and remained low for the whole study period ($P < 0{\cdot}01$) compared with controls. The splenic uptake rate of ^{125}I-radiolabelled bacteria increased immediately following subtotal hepatectomy

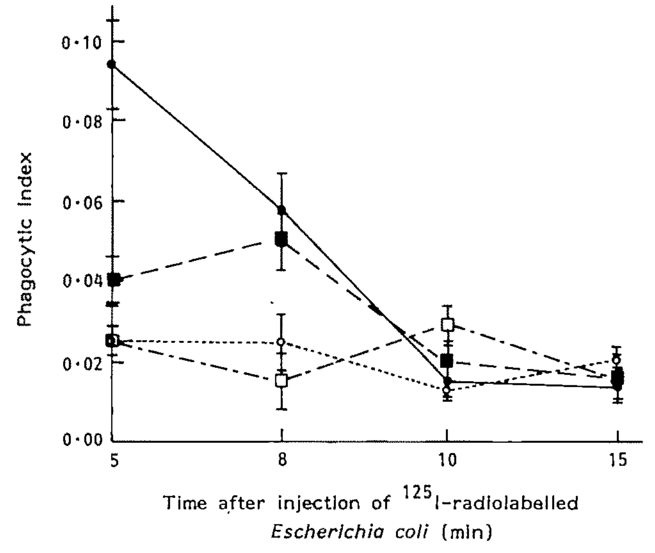

Figure 1 *Mean(s.e.m.) phagocytic index in control rats (sham operation, ●) and in rats 0 h (○), 2 h (■) and 6 h (□) after 90 per cent hepatectomy. Each group contained six animals*

Table 5 *Mean(s.e.m.) uptake rate and percentage distribution of ^{125}I-radiolabelled bacteria in various organs at different times after 90 per cent hepatectomy in the rat*

	Liver		Spleen		Lungs		Kidneys	
	Uptake rate (per g tissue)	Distribution (%)	Uptake rate (per g tissue)	Distribution (%)	Uptake rate (per g tissue)	Distribution (%)	Uptake rate (per g tissue)	Distribution (%)
Control (sham operation)	2·6(0·4)	87·7(0·4)	3·1(0·2)	9·9(0·4)	0·3(0·1)	1·5(0·2)	0·1(0·1)	0·9(0·1)
Time after operation (h)								
0	2·6(0·1)	25·4(1·4)†	5·5(0·3)*	31·1(2·2)†	2·8(0·2)*	34·5(2·2)†	0·3(0·0)*	7·8(0·6)†
2	3·6(0·5)	31·6(4·2)†	6·3(0·5)*	36·8(3·4)†	3·4(0·4)†	27·3(3·1)†	0·3(0·0)*	5·4(0·2)*
6	4·3(0·4)*	37·4(4·8)†	7·9(0·3)*	41·5(4·7)†	1·2(0·3)*	16·5(2·6)*	0·2(0·0)*	4·3(0·6)*

The uptake rate is the ratio of radioactivity per gram tissue to the total radioactivity intravenously injected, multiplied by 100. The distribution is the percentage uptake in each organ in proportion to total uptake in the four organs. Each group contained six rats. *$P < 0·05$; †$P < 0·01$ (*versus* control); Student's *t* test

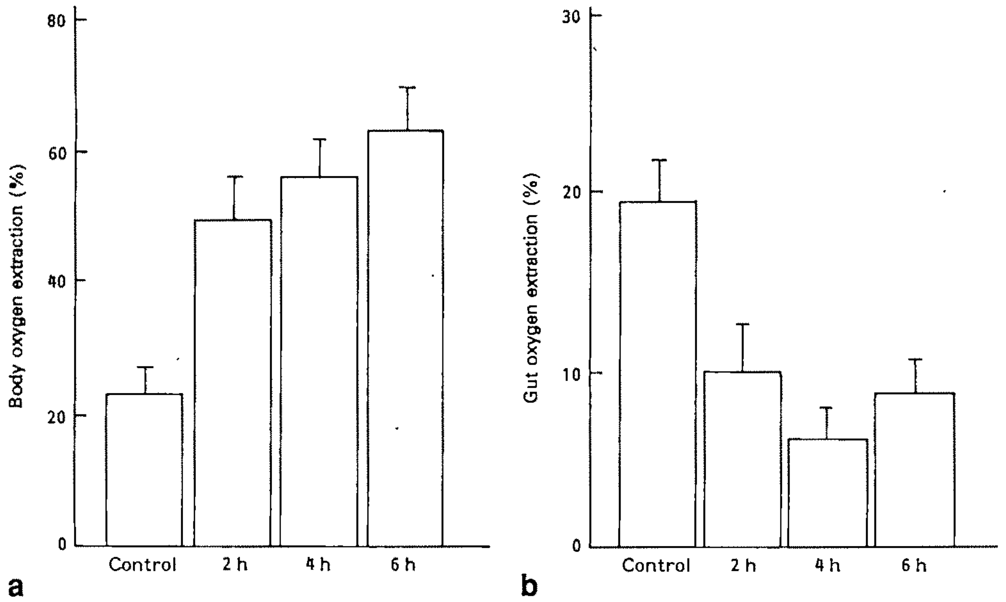

Figure 2 *Mean(s.e.m.)* **a** *whole-body and* **b** *gut oxygen extraction in control rats (sham operation) and rats at 2, 4 and 6 h after 90 per cent hepatectomy*

($P < 0·05$) and the percentage distribution increased during the study period compared with controls ($P < 0·01$). In both lungs and kidneys, radioactive uptake and percentage distribution increased immediately after hepatectomy.

Whole-body oxygen extraction in animals subjected to hepatectomy was significantly higher than in controls ($P < 0·01$) while no difference between the various times after hepatectomy was noted. In contrast, gut oxygen extraction in rats with 90 per cent hepatectomy significantly decreased 2, 4 and 6 h after operation ($P < 0·01$) (*Figure 2*).

Discussion

Bacterial infections and bacteraemia are serious complications frequently encountered in patients with acute liver failure[3,28,29]. Bacteraemia and bacterial infection have been suggested to aggravate other coexisting complications such as encephalopathy and liver dysfunction itself[28]. A defective host defence in acute liver failure, including impaired RES function[7] and decreased plasma levels of factors like fibronectin[30], opsonins and complement[8], might increase the occurrence of bacteraemia and infection. The exact origin and pathophysiological mechanisms underlying bacteraemia in such liver failure remain unclear.

The intestinal barrier has been defined as the first local defence[31]. Factors such as immune dysfunction of the host, age and fasting have been suggested to promote translocation of gut bacteria[13]. Therefore the study of bacterial translocation in acute liver failure induced by drugs[32] or hepatotoxic substances[33] may be affected by a possible influence on enteric bacteria by these substances themselves. Hence, 90 per cent subtotal hepatectomy in rats without any preoperative administration of hepatotoxic drugs was chosen as a model for induction of acute liver failure[19], which also has an associated increase in portal pressure (unpublished data).

In the present study, enteric bacteria were shown to translocate to blood, MLNs and other organs following 90 per cent hepatectomy, confirming observations in other experimental models[10,12,15]. The decrease in arterial blood pressure noted after 90 per cent hepatectomy could not be considered as a major factor influencing bacterial translocation in acute liver failure because blood pressure was kept at a similar level in controls. In experimental haemorrhagic shock[11], bacterial translocation occurred at a mean arterial pressure of 30 mmHg starting 2 h after induction of shock, followed by a significant bacteraemia uniformly appearing 3 h after. This suggests that bacterial translocation may be an acute event, and is not only a subacute or chronic process, as has been indicated previously[9,10]. According to the present results, bacterial translocation to blood and MLNs started 2 h after induction of acute liver failure. The predominantly isolated bacterium was *E. coli*, in accordance with findings in endotoxin-induced translocation[34], although *Pseudomonas aeruginosa* dominated in haemorrhagic shock-induced translocation[11]. In addition to *E. coli*, four other bacterial species were isolated from blood and organ cultures in rats with acute liver failure.

Many disorders in the gut have been attributed to bacterial overgrowth and colonization of the small intestine[35]. Bacterial adhesion to intestinal cell surfaces seems to be an important first step in enteric microbial overgrowth. Increased bacterial adhesion to the mucus layer and brush border after subtotal hepatectomy (unpublished data) might result in overgrowth and colonization[36], increasing the possibility of enteric bacteria penetrating the gut barrier to reach the MLNs. Aerobic bacterial overgrowth resulted in a selective loss of brush border alkaline phosphatase activity and an increase in γ-glutamyl transferase activity, while anaerobic overgrowth was related to a reduction in brush border density and the glycoprotein:lipid ratio of the brush border membrane[37]. The patterns of colonization have been reported to be influenced by the production of bacteriocines[38]. Bacterial overgrowth can be an important factor in acute liver failure in rats, increasing the risk of transfer of enteric microflora to blood and organs by disruption of the ecological balance in the intestine. Direct effects of bacterial proteases on specific microvillus membrane proteins[39] or impaired utilization of glutamine, the principal fuel of enterocytes[27], contribute to the breakdown of the intestinal barrier. Enteroinvasive *E. coli* not only invade intestinal endothelial cells, but also have the ability to release endotoxin and cytotoxin, which could injure the enterocytes[40]. In the present study gut oxygen utilization was impaired in acute liver failure induced by 90 per cent hepatectomy, indicating a decrease in gut metabolism, which might be one of the reasons explaining overgrowth of enteric microorganisms in liver failure. Another reason that should be considered is that a diminished bile secretion and/or disturbed enterohepatic circulation of bile acids in experimental acute liver failure induce dysfunction of the enterocytes and intestinal barrier as well as enteric bacterial overgrowth, since bile has an important trophic action in the gut[41] and also inhibits the growth of some enteric bacteria[42]. This study cannot eliminate the possibility that other more fastidious species of enteric bacteria, not isolated because of limitations in the culture facilities or techniques used, may take part in the disturbance of the intestinal barrier. A markedly diminished oxygen extraction in the intestine might be caused by opening of arteriovenous shunts thus diverting blood away from the gastrointestinal tract, which would result in altered intestinal function and structure, enhancing enteric bacterial translocation. This haemodynamic alteration in 90 per cent hepatectomy-induced acute liver failure may be attributed to portal hypertension, local tissue hypoxia, increased vasodilatation or reduced intestinal vascular resistance induced by toxins such as ammonia and endotoxin, as found in patients with chronic and fulminant liver failure[43]. A previous study[44] has demonstrated that blood flow in the liver remnant did not appear to fall in the early phase after subtotal hepatectomy, and no correlation between organ uptake and blood flow was noted.

The risk of bacterial invasion is increased with time after hepatectomy. The ability to clear bacteria decreased immediately following 90 per cent hepatectomy, although the phagocytic function in the spleen and lungs significantly increased. Spaeth *et al.*[45] recently reported that splenectomy reduced the incidence of endotoxin-induced bacterial translocation, probably due to a reduced response of distant organs to endoxotin. The present study found that the phagocytic activity of the spleen increased immediately after subtotal hepatectomy, while acute liver failure-induced bacterial translocation occurred 2 h later. These results support the possibility that some factors released from the spleen into the portal circulation might modulate circulating macrophages and Kupffer cells. According to the hypothesis of Wells *et al.*[16], submucosal macrophages phagocytose enteric bacteria that adhere to the mucus layer or invade the impaired intestinal barrier and 'carry' them through the intestinal wall after which the phagocytes liberate the phagocytosed bacteria. Alexander *et al.*[46] recently reported that intact large and small enteric bacteria and endotoxin pass directly through morphologically intact enterocytes. It is hypothesized[34] that overgrowth and colonization of small bowel by enteric bacteria in rats with acute liver failure induced by 90 per cent hepatectomy results in an increased release of endotoxin, promoting endotoxin or bacterial translocation and increasing xanthine dehydrogenase or oxidase activity, thereby damaging the intestinal mucosal barrier.

Haemodynamic and hormonal changes cannot be ruled out as possible contributory mechanisms explaining bacterial translocation induced by acute liver failure. Hypotension in patients with fulminant liver failure has been observed[47] as well as in rats with 90 per cent hepatectomy-induced acute liver failure in the present study. Haemodynamic changes and multiple organ failure following liver failure were related to vasodilatation locally increasing intestinal permeability[43]. Changes in portal vein circulation after 90 per cent hepatectomy should be taken into consideration since a reduction in the portal run-off occurs after hepatectomy similar to that seen in liver cirrhosis. Although the pressure and blood flow in the portal vein were not determined in the present study, such changes are to be expected. Portal hypertension might result in extravasation from intestinal veins and oedema, inducing an increase in intestinal permeability. Furthermore, the concentrations of substances such as prostaglandins, various gastrointestinal peptides, tumour necrosis factor, γ-aminobutyric acid and ammonia might also increase and influence permeability.

In conclusion, enteric bacteria, especially *E. coli*, translocated to blood and MLNs 2 h after 90 per cent hepatectomy and increased in blood and organs with time after the operation. An overgrowth of *E. coli* in the small intestine and a decreased RES function were noted. Thus, bacterial translocation was evident in the early phase of acute liver failure induced by 90 per cent hepatectomy.

References

1. Larcher VF, Wyke RJ, Mowat AP, Williams R. Bacterial and fungal infection in children with fulminant hepatic failure: possible role of opsonisation and complement deficiency. *Gut* 1982; **23**: 1037–43.
2. Williams R, Gimson AES. Management of acute liver failure. *Clinical Gastroenterology* 1985; **14**: 93–104.
3. Rolando N, Harvey F, Brahm J *et al.* Prospective study of bacterial infection in acute liver failure: an analysis of fifty patients. *Hepatology* 1990; **11**: 49–53.
4. Albright JW, Matusewicz NM, Albright JF. Aging of the murine immune system is reflected by declining ability to generate antibodies that promote elimination of *Trypanosoma musculi. J Immunol* 1988; **141**: 1318–25.
5. Friedman RL, Moon RJ. Role of Kupffer cells, complement, and specific antibody in the bactericidal activities of perfused liver. *Infect Immun* 1980; **29**: 152–7.
6. Sawyer RT, Moon RJ, Beneke ES. Hepatic clearance of *Candida albicans* in rats. *Infect Immun* 1976; **14**: 1348–65.
7. Canalese J, Gove CD, Gimson AES, Wilkinson SP, Wardle EN, Williams R. Reticuloendothelial system and hepatocyte function in fulminant hepatic failure. *Gut* 1982; **23**: 265–9.
8. Wyke RJ, Rajkovic IA, Eddleston ALWF, Williams R. Defective opsonisation and complement deficiency in serum from patients with fulminant hepatic failure. *Gut* 1980; **21**: 643–9.
9. Berg RD, Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. *Infect Immun* 1979; **23**: 403–11.
10. Rush BF, Redan JA, Flanagan JJ *et al.* Does the bacteremia observed in hemorrhagic shock have clinical significance? A study in germ-free animals. *Ann Surg* 1989; **210**: 342–7.
11. Koziol JM, Rush BF, Smith SM, Machiedo GM. Occurrence of bacteremia during and after hemorrhagic shock. *J Trauma* 1988; **28**: 10–16.
12. Deitch EA, Li M, Jing-wen M, Berg RD. Lethal burn-induced bacterial translocation: role of genetic resistance. *J Trauma* 1989; **29**: 1480–7.
13. Deitch EA, Berg R, Specian R. Endotoxin promotes the

translocation of bacteria from the gut. *Arch Surg* 1987; **122**: 185–90.
14. Alverdy JC, Aoys E, Moss GS. Total parenteral nutrition promotes bacterial translocation from the gut. *Surgery* 1988; **104**: 185–90.
15. Deitch EA, Wen-jing M, Li M, Rodney D, Specian D. Protein malnutrition predisposes to inflammatory-induced gut-origin septic states. *Ann Surg* 1990; **211**: 560–8.
16. Wells CL, Maddaus MA, Simmons RL. Proposed mechanisms for the translocation of intestinal bacteria. *Rev Infect Dis* 1988; **10**: 958–78.
17. Sori AJ, Rush BF, Lysz TW, Smith S, Machiedo GW. The gut as a source of sepsis after hemorrhagic shock. *Am J Surg* 1988; **155**: 187–92.
18. Berg RD. Translocation of indigenous bacteria from the intestinal tract. In: Hentges DJ, ed. *Human Intestinal Microflora in Health and Disease*. New York: Academic Press, 1983: 333–52.
19. Demetriou AA, Reisner A, Sanchez J, Levenson SM, Moscioni AD, Chowdhury JR. Transplantation of microcarrier-attached hepatocytes into 90% partially hepatectomized rats. *Hepatology* 1988; **8**: 1006–9.
20. Wang XD, Ar' Rajab A, Ahrén B, Andersson R, Bengmark S. Co-transplantation with pancreatic islets improves the effect of intrasplenic transplantation of hepatocytes after 90% hepatectomy in the rat. *Transplantation* 1991; **52**: 462–6.
21. Deitch EA, Maejima K, Berg R. Effect of oral antibiotics and bacterial overgrowth on the translocation of the GI tract microflora in burned rats. *J Trauma* 1985; **25**: 385–92.
22. Holdeman LV, Cato EP, Moore WEC. *Anaerobe Laboratory Manual*. Blacksburg: Virginia Polytechnic Institute, 1977.
23. Lennette EH. *Manual of Clinical Microbiology*. Washington, District of Columbia, American Society for Microbiology, 1985.
24. McConahey PJ, Dixon FJ. A method of trace iodination of proteins for immunological studies. *Int Arch Allergy Appl Immunol* 1966; **29**: 185–8.
25. Braude AI, Carey FJ, Sutherland D, Zalesky M. Studies with radioactive endotoxin of *Escherichia coli*. *J Clin Invest* 1955; **34**: 850–4.
26. Arii S, Monden K, Itai S, Sasaoki T, Shibagaki M, Tobe T. The three different phases of reticuloendothelial system phagocytic function in rats with liver injury. *J Surg Res* 1988; **45**: 315–19.
27. Salloum RM, Plumley DA, Flynn TC, Copeland EM. The effects of sepsis and endotoxemia on gut glutamine metabolism. *Ann Surg* 1990; **5**: 543–51.
28. Wyke RJ. Bacterial infection complicating liver disease. *Baillieres Clin Gastroenterol* 1989; **3**: 187–210.
29. Wyke RJ, Canalese JC, Gimson AES. Bacteraemia in patients with fulminant hepatic failure. *Liver* 1983; **2**: 45–52.
30. Anand AC, Irshad M, Acharya SK, Gandhi BM, Joshi YK, Tandon BN. Fibronectin in acute and subacute hepatic failure. *J Clin Gastroenterol* 1989; **11**: 314–19.
31. Rhodes RS, Depalma RG, Robinson AV. Intestinal barrier function in hemorrhagic shock. *J Surg Res* 1973; **14**: 305–12.
32. Butler J, Weise V, Kopin J *et al*. A mode of fulminant hepatic failure in the rabbit. *Gastroenterology* 1978; **74**: 664–71.
33. Panella C, Makowka L, Barone M *et al*. Effect of ranitidine on acetaminophen-induced hepatotoxicity in dogs. *Dig Dis Sci* 1990; **35**: 385–91.
34. Deitch EA, Taylor M, Grisham M, Li M, Bridges W, Berg R. Endotoxin induces bacterial translocation and increases xanthine oxidase activity. *J Trauma* 1989; **29**: 1679–83.
35. King CE, Toskes PP. Small intestine bacterial overgrowth. *Gastroenterology* 1979; **76**: 1035–55.
36. Schlager TA, Wanke CA, Guerrant RL. Fluid secretion and impaired villous function induced by colonization of the small intestine by nontoxigenic colonizing *Escherichia coli*. *Infect Immun* 1990; **58**: 1337–43.
37. Batt RM, Melean L. Comparison of the biochemical changes in the jejunal mucosa of dogs with aerobic and anaerobic bacterial overgrowth. *Gastroenterology* 1987; **93**: 986–93.
38. Bagg J. Can the colonisation resistance of the oral microflora be reduced? *Microbial Ecology in Health and Disease* 1990; **3**: 5–8.
39. Riepe SP, Goldstein J, Alpers DH. Effect of secreted bacteroid proteases on human intestinal brush border hydrolases. *J Clin Invest* 1980; **66**: 314–22.
40. Fasano A, Kay BA, Russell RG, Maneval DR, Levine MM. Enterotoxin and cytotoxin production by enteroinvasive *Escherichia coli*. *Infect Immun* 1990; **58**: 3717–23.
41. Borghi AF, Petrino R, Bargoni A, Fronticelli CM, Gentilli S. Modifications of the trophism of intestinal mucosa after intestinal and bilio-pancreatic diversion in the rat. *Ital J Gastroenterol* 1991; **23**: 202–7.
42. Floch MH, Gershengoren W, Eliott S, Spiro HM. Bile acid inhibition of the intestinal microflora – a function for simple bile acids? *Gastroenterology* 1971; **61**: 228–33.
43. Sherlock S. Vasodilatation associated with hepatocellular disease: relation to fulminant organ failure. *Gut* 1990; **31**: 365–7.
44. Wang XD, Andersson R, Ding JW, Norgren L, Bengmark S. Reticuloendothelial system function following acute liver failure induced by 90% hepatectomy in the rat. *HPB Surg* 1992 (in press).
45. Spaeth G, Specian RD, Berg RD, Deitch EA. Splenectomy influences endotoxin-induced bacterial translocation. *J Trauma* 1990; **30**: 1267–72.
46. Alexander JW, Boyce ST, Babcock GH *et al*. The process of microbial translocation. *Ann Surg* 1990; **212**: 496–511.
47. Trewby PN, Williams R. Pathophysiology of hypotension in patients with fulminant liver failure. *Gut* 1977; **18**: 1021–6.

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Histamine but neither angiotensin nor vasopressin increases antibody uptake into xenograft colorectal liver metastases

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Although the majority of colorectal carcinomas express carcinoembryonic antigen (CEA), systemic anti-CEA antibody administration is an ineffective treatment for colorectal liver metastasis. A xenograft model of human colorectal carcinoma in the rat was used to determine anti-CEA antibody uptake into liver metastases. The influence of systemic (iliolumbar vein) or regional (gastroduodenal artery) delivery and effects of regional delivery of histamine, angiotensin II and vasopressin on anti-CEA antibody uptake by metastases were examined. Systemic antibody delivery achieved a median tumour:liver antibody uptake ratio of 1·60 (interquartile range (i.q.r.) 1·02–2·51). Regional delivery resulted in a similar median ratio of 1·61 (i.q.r. 1·22–2·46). Histamine and antibody delivered regionally produced a median tumour:liver ratio of 3·15 (i.q.r. 2·50–4·27), which was significantly greater than that obtained with systemic delivery (P = *0·004). Regional infusion of angiotensin resulted in a median (i.q.r.) ratio of 2·23 (1·58–2·49) and vasopressin in 2·15 (1·41–2·60), values that were not significantly different from those found with systemic or regional delivery alone. When both angiotensin and histamine were infused with antibody, the median tumour:liver ratio was 3·09 (i.q.r. 2·22–4·31), significantly greater than for systemic delivery* (P = *0·01) but not significantly different from that obtained following the addition of histamine alone* (P = *0·94). Histamine significantly increases antibody uptake in a model of liver metastasis and may improve the effectiveness of targeted immunotherapy in the treatment of colorectal liver metastasis.*

Liver metastases develop in approximately 30 per cent of patients who undergo curative excision of colorectal carcinoma and are present in most whose cancers are incurable at primary diagnosis[1]. Dissemination to extrahepatic sites such as lung and bone is frequently by secondary metastasis from deposits that have already developed within the liver[2]. Therefore, control of liver metastases, both established and occult, is important in colorectal carcinoma.

Expression of carcinoembryonic antigen (CEA) by the majority of colorectal carcinomas[3] makes antibody-targeted treatment attractive. Unfortunately, this approach usually has little effect because insufficient antibody is taken up by tumour after systemic administration of radiolabelled antibody[4]. The passage of circulating antibody into the extracellular space depends on the intravascular dose, capillary permeability[5,6] and tumour blood flow[7]. The aim of this study was to determine the potential for manipulating each of these factors to increase tumour antibody uptake in an experimental model.

First, an increase in intravascular dose was achieved by regional delivery of antibody into the hepatic artery, which increased the antibody concentration delivered to the tumours. Second, histamine[8] was used to alter capillary permeability. Finally, because tumour capillaries are devoid of smooth muscle[9], the effects of the vasoconstrictor agents angiotensin II[10] and vasopressin[11], which divert blood flow from normal liver to tumour, were studied.

To examine these approaches a xenograft model of a CEA-expressing human colorectal liver metastasis in the rat was developed.

Materials and methods

Anti-CEA antibody (A5B7) was labelled with iodine-131 using the chloramine T method[12]. Genetically immunocompromised PVG homozygous nude rats, weight 150–200 g (Department of Comparative Biology, Charing Cross and Westminster Medical School, London, UK), were maintained in a negative-pressure isolator (Isotec, Bicester, UK) and fed on sterile water and solids *ad libitum*. A total of 10^6 cells from a human colonic cancer cell line (LS174T) in 0·1 ml complete medium (Gibco, Uxbridge, UK) were injected subcutaneously into the mid-thigh of the hindlimb. Once solid tumours had grown, the tumour line was serially passaged. Under general anaesthesia with nitrous oxide and halothane (0–0·5 per cent in oxygen) a midline laparotomy incision was made and diced fragments of these tumours (mean weight 25 mg) implanted into the right lobe of the liver.

After a tumour growth period of 4 weeks, the animal was anaesthetized. The midline incision was reopened to confirm the presence of liver tumour and to expose the porta hepatis, gastroduodenal artery, hepatic artery and inferior vena cava. Two cannulas (Portex 0·6 mm external diameter; Arterial Medical Supplies, London, UK) were inserted under direct vision using an operating microscope.

The first ('venous' or 'systemic') cannula was inserted into the right iliolumbar vein so that its tip lay at the junction of the iliolumbar vein and inferior vena cava, allowing access to the systemic circulation. The second ('arterial' or 'regional') cannula was passed retrogradely into the gastroduodenal artery so that its tip lay at the junction with the hepatic artery to gain access to the arterial supply of the tumour-bearing liver while preserving hepatic artery flow. Arteriography confirmed that the entire liver was perfused (*Figure 1*).

Antibody infusions were carried out over 1 h. All infusions contained 40 μg radiolabelled antibody in 0·5 ml phosphate buffer to which was

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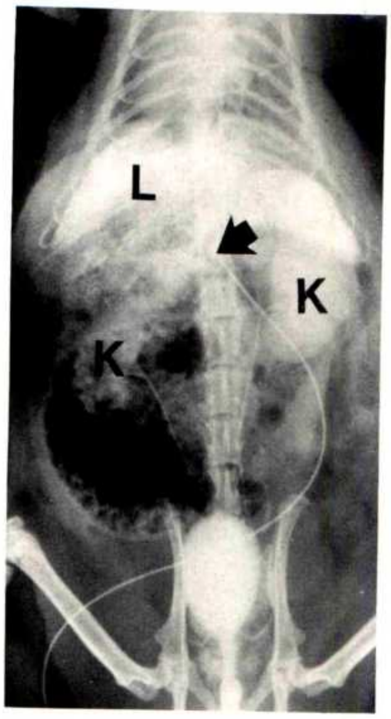

Figure 1 *Arteriogram performed through a gastroduodenal artery cannula (arrow). All of the liver (L) has filled with contrast supplied via the cannula. The kidneys (K) have been filled with excreted contrast*

added 0·5 ml phosphate buffer either unaltered or containing histamine, angiotensin, vasopressin or both angiotensin and histamine (all from Sigma Chemicals, Poole, UK). In 11 rats anti-CEA antibody was delivered into the systemic cannula with an infusion of saline (1 ml) delivered regionally. In a further 11 animals antibody was delivered regionally and saline systemically. In 34 rats the radiolabelled antibody was mixed with either histamine (5 mg/kg; $n = 10$), angiotensin II (20 μg/kg; $n = 12$) or vasopressin (10 milliunits/kg; $n = 12$) and then delivered regionally. In a further ten animals the antibody was mixed with both angiotensin and histamine at the same dose as above and then infused regionally. The solutions of drug and antibody were prepared in phosphate buffer at pH 7·4.

After infusion, the cannulas were removed, carefully preserving flow to the tumour-bearing liver, the abdomen was closed and the animal allowed to recover. After 48 h, the rat was anaesthetized and the liver and tumour excised and weighed. Gamma emissions were measured in a well counter (Minaxi AutoGamma 5000; Canberra Packard, Pangbourne, UK; well-counter window settings 260–470 keV) to determine the ratio of tumour:liver γ counts per gram tissue.

In a separate group of five animals, the tumour:liver ratio was measured in multiple tumour samples after regional delivery alone; the variation in the γ emissions per gram tumour was <6 per cent.

Data were analysed using Kruskal–Wallis analysis of variance and the Mann–Whitney U test. $P < 0.05$ was considered significant.

Results

The tumour:liver ratios of γ emissions measured in each group are shown in *Figure 2*. There were significant overall differences between the groups ($H = 17.3$, $P = 0.004$, Kruskal–Wallis test).

Systemic delivery achieved a median tumour:liver ratio of 1·60 (interquartile range (i.q.r.) 1·02–2·51). Regional delivery resulted in a nearly identical ratio of 1·61 (i.q.r. 1·22–2·46) ($P = 0.82$).

Histamine added to the antibody and delivered regionally produced a median tumour:liver ratio of 3·15 (i.q.r. 2·50–4·27), significantly greater than that obtained after regional ($P = 0.02$) and systemic ($P = 0.004$) delivery alone. The ratios obtained after addition of angiotensin II (median 2·23 (i.q.r. 1·58–2·49)) or vasopressin (median 2·15 (i.q.r. 1·41–2·60)) were not significantly different from that found after systemic (angiotensin, $P = 0.12$; vasopressin, $P = 0.31$) or regional ($P = 0.16$, $P = 0.39$) antibody delivery alone.

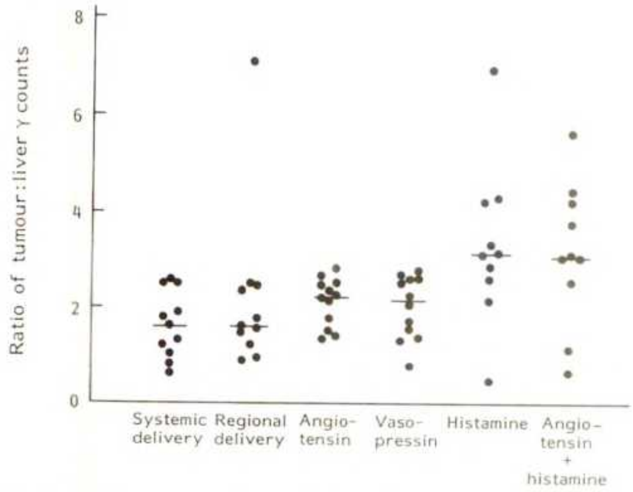

Figure 2 *Tumour:liver ratios of γ emissions. Bars are medians*

When both angiotensin and histamine were administered the median tumour:liver ratio was 3·09 (i.q.r. 2·22–4·31). This was significantly greater than that found with systemic ($P = 0.01$) or regional ($P = 0.05$) antibody delivery but not significantly different from that obtained following regional administration of antibody with histamine alone ($P = 0.94$).

Discussion

This model of hepatic metastases has several similarities with human colorectal metastases to the liver, despite the different route of administration of neoplastic cells to the liver. The metastases produced derive their blood supply from the hepatic artery and appear as pale solid masses in the liver. On histological examination they resemble human liver metastases.

Regional administration of radiolabelled antibody did not increase the ratio of tumour:liver counts compared with systemic delivery. It is known that the first-pass extraction of antibodies is low[13] and that the advantages of regional delivery are greatest where there is a high first-pass extraction[14]. Thus there appears to be no benefit in regional delivery of antibody alone.

Histamine, which increases capillary permeability in normal tissues, approximately doubled the ratio of tumour:liver antibody uptake. The mechanism for this might not necessarily be a change in capillary permeability. However, a previous study showed a similar effect in extrahepatic tumours using other capillary permeability agents that have differing vasoactive properties[15]. Therefore, it appears that tumour capillaries are susceptible to pharmacologically initiated changes in permeability to macromolecules, and that this change can increase tumour antibody uptake.

Administration of angiotensin can increase the tumour:liver uptake ratio of low molecular weight agents[10,16] that have a high first-pass extraction. Angiotensin can also increase the uptake of microspheres by colorectal liver metastases[17] compared with the surrounding normal tissue. Angiotensin administered with 5-fluorouracil may prolong survival[18]. However, vasoconstrictor agents did not increase the tumour:liver antibody uptake ratio in the present study.

Blood flow changes induced in the liver by angiotensin last for only a few minutes[19,20]. This may explain the inability of angiotensin or vasopressin to increase antibody uptake and the inability of angiotensin to influence the effect of histamine. The first-pass extraction of antibodies is low and so transport out of the microcirculation is slow. Therefore, a more sustained period of flow alteration may be required to increase antibody transport from blood to tissue.

The action of vasoconstrictors is usually related to the systemic effects on blood pressure, resulting in vasoconstriction in the liver but not in the tumour vessels, which have no smooth muscle. The doses of angiotensin and vasopressin in this study were selected to have a local effect without producing potentially lethal systemic hypertension. The use of this lower dose may explain the lack of a vasoconstrictor-induced effect on antibody uptake.

It has been suggested that a tenfold increase in tumour:liver antibody concentration is required for treatment with radiolabelled antibody to be effective[21], although a threefold rise may be sufficient in some patients[4]. The present study shows that regional delivery of histamine with radiolabelled anti-CEA antibody doubles the tumour:liver ratio. Regional delivery of antibody alone confers no advantage. Vasoconstrictor manipulation was ineffective in this study, but if a longer period of vasoconstriction could be achieved additional improvement in tumour uptake might be possible.

To date, radiolabelled antibodies cannot achieve sufficient concentration in tumour tissue to be useful in treatment. Pharmacological manipulation of the tumour circulation could be one of the strategies that may make treatment with radiolabelled antibodies a realistic proposition.

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References

1. Greenway B. Hepatic metastases from colorectal cancer: resection or not. *Br J Surg* 1988; **75**: 513–19.
2. Weiss L, Grundman E, Torhorst J *et al.* Haematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. *J Pathol* 1986; **150**: 195–203.
3. Crowson MC, Hockey MS, Newman J, Stokes H, Macdonald F, Fielding JWL. An immunocytochemical study of carcinoembryonic antigen (CEA) expression in colorectal tumours and their metastases using a monoclonal antibody. *Br J Surg* 1984; **71**: 376 (Abstract).
4. Begent RHJ, Lederman JA, Green AJ *et al.* Antibody dosimetry in patients receiving radiolabelled antibody therapy for colorectal cancer. *Br J Cancer* 1989; **60**: 406–12.
5. Sands H, Jones PL, Neacy WP, Shah SA, Gallagher BM. Site-related differences in the localisation of the monoclonal antibody OX7 in the SL2 and SL1 lymphomas. *Cancer Immunol Immunother* 1986; **22**: 169–75.
6. Sands PH, Shah SA, Gallagher BM. Vascular volume and permeability of human and murine tumours in athymic mice. *Cancer Lett* 1985; **27**: 15–21.
7. Sands PH, Jones PL, Shah SA, Palme D, Vessella RL, Gallagher BM. Correlation of vascular permeability and blood flow with monoclonal antibody uptake by human Clouser and renal cell xenografts. *Cancer Res* 1988; **48**: 188–93.
8. Majno G, Shea SM, Levanthal M. Endothelial contraction induced by histamine-type mediators: an electron microscope study. *J Cell Biol* 1969; **42**: 647–72.
9. Krylova NV. Characteristics of microcirculation in experimental tumours. *Bibl Anat* 1969; **10**: 301–3.
10. Susuki M, Hori K, Abe I, Saito S, Sato H. A new approach to cancer chemotherapy: selective enhancement of tumour blood flow with angiotensin II. *J Natl Cancer Inst* 1981; **67**: 663–9.
11. Ekelund L, Gothlin J, Jonsson N, Sjogren HO. Pharmacoangiography in experimental tumours. *Acta Radiol Diagn* 1976; **17**: 329–42.
12. Greenwood FC, Hunter WM, Glover JS. The preparation of ^{131}I-labelled human growth hormone of high specific radioactivity. *Biochem J* 1963; **89**: 114–23.
13. Steinstrasser A, Lappe F, Schwarz A, Kuhlman L. Radioimmunotherapy – selection of nuclides. *Eur J Nucl Med* 1988; **14**: 330.
14. Dedrick RL. Arterial drug infusion: pharmacokinetic problems and pitfalls. *J Natl Cancer Inst* 1988; **80**: 84–9.
15. Hennigan TW, Begent RHJ, Allen-Mersh TG. Histamine, leukotriene C4 and interleukin-2 increase antibody uptake into a human carcinoma xenograft model. *Br J Cancer* 1991; **64**: 872–4.
16. Hemingway DM, Cooke TG, Chang D, Grime SJ, Jenkins SA. The effects of intra-arterial vasoconstrictors on the distribution of a radiolabelled low molecular weight marker in an experimental model of liver tumour. *Br J Cancer* 1991; **63**: 495–8.
17. Goldberg JA, Murray T, Kerr DJ *et al.* The use of angiotensin II as a potential method of targeting cytotoxic microspheres in patients with intrahepatic tumour. *Br J Cancer* 1991; **63**: 308–10.
18. Goldberg JA, Kerr DJ, Wilmott N, McKillop JH, McArdle CS. Regional chemotherapy for colorectal liver metastases: a phase II evaluation of targeted hepatic arterial 5-fluorouracil for colorectal liver metastases. *Br J Surg* 1990; **77**: 1238–40.
19. Henningan TW, Allen-Mersh TG. Duration of action of vasoconstrictor agents on liver blood flow. *Br J Surg* 1991; **78**: 756 (Abstract).
20. Sasaki Y, Imaoka S, Hasegawa Y *et al.* Changes in distribution of hepatic blood flow induced by intra-arterial infusion of angiotensin II in human hepatic cancer. *Cancer* 1985; **55**: 311–16.
21. Dykes PW, Bradwell AR, Chapman CE, Vaughan ATM. Radioimmunotherapy of cancer: clinical studies and limiting factors. *Cancer Treat Rev* 1987; **14**: 87–106.

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Controlled liver splitting for transplantation in two recipients: technique, results and perspectives

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A technique of controlled liver splitting for transplantation in two recipients is proposed, based on a full anatomical assessment of the graft including arteriography and cholangiography on the back-table. Using eight livers, 16 patients received a graft: right liver (eight patients), left lobe (four) or left liver (four). Twelve patients required urgent or very urgent transplantation. Anatomical assessment of the graft demonstrated a portal bifurcation in all cases, a common trunk of the left and middle hepatic veins in five, a right biliary duplication in three and duplication of the left branch of the middle hepatic artery in one. After revascularization of the graft, bleeding was greater in patients with a right graft, particularly if the middle hepatic vein had been ligated. The main postoperative complications were hepatic artery thrombosis (four cases), biliary complications (four), portal vein thrombosis (two), haematoma (two) and abscess (two). No primary non-function of the graft was observed. The postoperative survival rate was 75 per cent. The four patients in whom transplantation was not considered urgent are still alive. The immediate survival rate of the grafts was 69 per cent. These results compare favourably with those in the literature. In spite of the technical, logistical and ethical problems raised by this technique, the results suggest that controlled liver splitting for transplantation in two recipients may in the future significantly improve the feasibility of liver transplantation.

Because of improvement in results, liver transplantation has been increasingly offered to patients with severe hepatic disease. There is an imbalance between the number of cadaveric liver grafts and the number of patients waiting for a transplant. To reduce the time that patients have to wait for a graft and the consequent risks, it is essential to find more grafts.

After the description[1–3] and successful development[4–6] of techniques of volume reduction of liver grafts from adults for transplantation in children, it appeared that, in some cases, the right part of the graft could perhaps be retained for another recipient. The initial attempt to treat two recipients with one donor organ was made by Pichlmayr *et al.*[7]. In the first reported series[8–10] the graft survival rate was disappointingly low. Assuming that several postoperative complications might be related to undetected anatomical variations, two of the present authors performed a detailed anatomical study and proposed a technique of controlled liver splitting[11]. Opacification of the arterial and biliary trees allows identification of numerous possible anatomical variations. This led to the first successful clinical application of this technique in two children[12]. The technical aspects, surgical complications and overall results of a series of 16 patients who received a graft after controlled liver splitting are now reported.

Patients and methods

Eight livers from heart-beating cadaveric donors underwent controlled liver splitting and were grafted into 16 recipients. Seven controlled liver splitting operations and 14 transplantations were performed at Cochin Hospital by one surgeon (D.H.). One operation and the two corresponding transplantations were carried out using the same technique at Edouard Herriot Hospital by another surgeon (O.B.). Fourteen recipients received primary transplants.

Recipients

The main characteristics of the recipients are shown in *Table 1*. There were ten children and six adults.

In four cases, both recipients were in a very precarious condition: at least one of the two recipients was in the France-Transplant 'superurgent' category because of fulminant hepatitis or early failure of a first graft.

In the four other procedures the need for transplantation in one of the recipients was not urgent but the patient had reached first position on the France-Transplant waiting list, whereas the second recipient required rapid transplantation for recently diagnosed end-stage chronic liver disease. According to the France-Transplant 'first come, first served' rule which, apart from the superurgent category, was operating at that time for all recipients, the graft was specifically attributed to the non-urgent patient who was in first position on the list. This opportunity was taken to offer liver transplantation to the additional four patients in urgent need because of end-stage chronic liver disease. All patients or their guardians gave informed consent to the use of liver obtained by controlled splitting.

Working organization

Work started early in the day. Patient A, to whom the graft was specifically attributed, was the first to enter the operating room (A). While a first surgical team (A) began the operation, the feasibility of controlled liver splitting was assessed in operating room B by the senior surgeon. When splitting was complete, patient B entered operating room B and the operation was started by surgical team B after revascularization of the graft in patient A. Removal of the diseased liver in patient B was performed only after the main vascular steps had been achieved in patient A.

Anatomical assessment of grafts and surgical technique of controlled liver splitting

The first step was identification of the bifurcation of the portal vein by dissection of the posterior wall of the main portal vein. Next the hepatic veins were inspected and probed (step 2). The common bile duct was opacified (step 3) on the back-table by injection of a few drops of amidotrizoate (Radioselectan; Schering, Paris, France) contrast medium at 4°C into the bile duct. Opacification was limited to the first- and second-order branches. The contrast was then immediately flushed out with cold University of Wisconsin (UW) solution. In step 4, a few millilitres of the same contrast medium were injected into the

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Table 1 *Details of the eight pairs* of recipients*

Patient no.	Age (years)	Sex	Body-weight (kg)	Liver disease	Status before transplantation	Urgency of transplantation	Date of transplantation
1A	3	F	13	Biliary atresia	At home	Not urgent	26 March 1990
1B	13	M	33	Byler's disease	In hospital	Urgent	
2A	1	M	10	Primary graft non-function	In ICU	Very urgent	3 October 1990
2B	46	F	77	Posthepatitis cirrhosis	In ICU	Urgent	
3A	9	M	19	Alagille syndrome	At home	Not urgent	12 January 1991
3B	46	M	70	Posthepatitis C cirrhosis	In ICU	Urgent	
4A	10	M	30	Fulminant Wilson's disease	In ICU	Very urgent	11 February 1991
4B	1	M	9	Hepatic artery and portal vein thrombosis of first graft	In ICU	Very urgent	
5A	14	F	50	Fulminant Wilson's disease	In ICU	Very urgent	15 March 1991
5B	42	F	65	Posthepatitis B and δ cirrhosis	In hospital	Urgent	
6A	40	F	86	Autoimmune hepatitis	At home	Not urgent	7 June 1991
6B	13	M	21	Sclerosing cholangitis	In ICU	Very urgent	
7A	40	M	67	Sclerosing cholangitis	At home	Not urgent	27 September 1991
7B	2	M	16	α_1-antitrypsin deficiency	In hospital	Very urgent	
8A	8	M	25	Fulminant hepatitis	In ICU	Very urgent	13 November 1991
8B	48	F	78	Fulminant hepatitis (mushroom)	In ICU	Very urgent	

ICU, intensive care unit. *In each pair the first patient is the one to whom the graft was initially given

Table 2 *Anatomical assessment of eight liver allografts before splitting and transplantation in 16 recipients after variable cold ischaemia times*

		Anatomical assessment of donor liver				Recipients*			
CLS no.	Donor body-weight (kg)	Hepatic veins	Portal vein bifurcation	Left and right bile ducts	Hepatic artery	No.	Body-weight (kg)	Type of graft†	Cold ischaemia time
1	80	Common trunk of MHV and LHV	Present	No duplication	Middle hepatic artery, left duplication	1A	13	Right liver	7 h 45 min
						1B	33	Left lobe	14 h 30 min
2	75	Separate MHV and LHV	Present	Right duplication	Middle hepatic artery, no duplication	2A	10	Left lobe	6 h
						2B	77	Right liver	14 h
3	70	Common trunk of MHV and LHV	Present	Right duplication	Right hepatic artery, no duplication	3A	19	Left liver	9 h
						3B	70	Right liver	19 h 45 min
4	55	Separate MHV and LHV	Present	Right duplication	Middle and left hepatic arteries, no duplication	4A	30	Right liver	8 h
						4B	9	Left lobe	10 h 30 min
5	73	Common trunk of MHV and LHV	Present	No duplication	Middle hepatic artery, no duplication	5A	50	Left liver	11 h
						5B	65	Right liver	17 h 45 min
6	70	Common trunk of MHV and LHV	Present	No duplication	Middle hepatic artery, no duplication	6A	86	Right liver	15 h
						6B	21	Left liver	19 h
7	65	Common trunk of MHV and LHV	Present	No duplication	Middle hepatic artery, no duplication	7A	67	Right liver	13 h
						7B	16	Left lobe	15 h 30 min
8	65	Separate MHV and LHV	Present	No duplication	Middle hepatic artery, no duplication	8A	25	Left liver	7 h 30 min
						8B	78	Right liver	13 h 30 min

MHV, middle hepatic vein; LHV, left hepatic vein. *In each pair the first patient is the one to whom the graft was initially given. †Right liver: segments V, VI, VII and VIII; left lobe: segments II and III; left liver: segments II, III and IV

artery for opacification of the first- and second-order arterial branches and then immediately flushed out using cold UW solution.

Shaping of the grafts (step 5) was carried out on the back-table by transecting the parenchyma with a forceps. Haemostasis and biliostasis of the transected areas were completed with 5 ml biological glue (Biocol; Biotransfusion, Lille, France).

Transplantation technique, postoperative care and assessment of results

All grafts were protected from ischaemia using UW solution and transplanted orthotopically. The inferior vena cava was retained in recipients of the left graft. During operation, the amount of bleeding after revascularization of the graft was calculated from the volume of allogeneic and autologous red blood cells transfused during the postanhepatic phase of transplantation. Standard immunosuppression was instituted after operation using cyclosporin and steroids. The type and number of postoperative surgical complications were recorded, as well as graft rejection, graft survival and patient survival rates.

Results

Anatomical assessment of the grafts and controlled liver splitting (Table 2) (Figure 1)

Step 1. A portal vein bifurcation was present in all eight cases. In seven the main portal vein was retained with the left graft, to bridge more easily the greater distance to the recipient's portal vein that results from the necessary rotation of the left graft to the right. In one case (CLS6) the portal vein was retained with the right graft because of a thrombosis of the recipient's portal vein that required thrombectomy and tailoring of the vein.

Step 2. In five cases there was a short common trunk of the middle and left hepatic veins. In CLS3, a large branch from segment VIII ended in the middle hepatic vein; in CLS6, a large branch from segment IV ended in a small middle hepatic

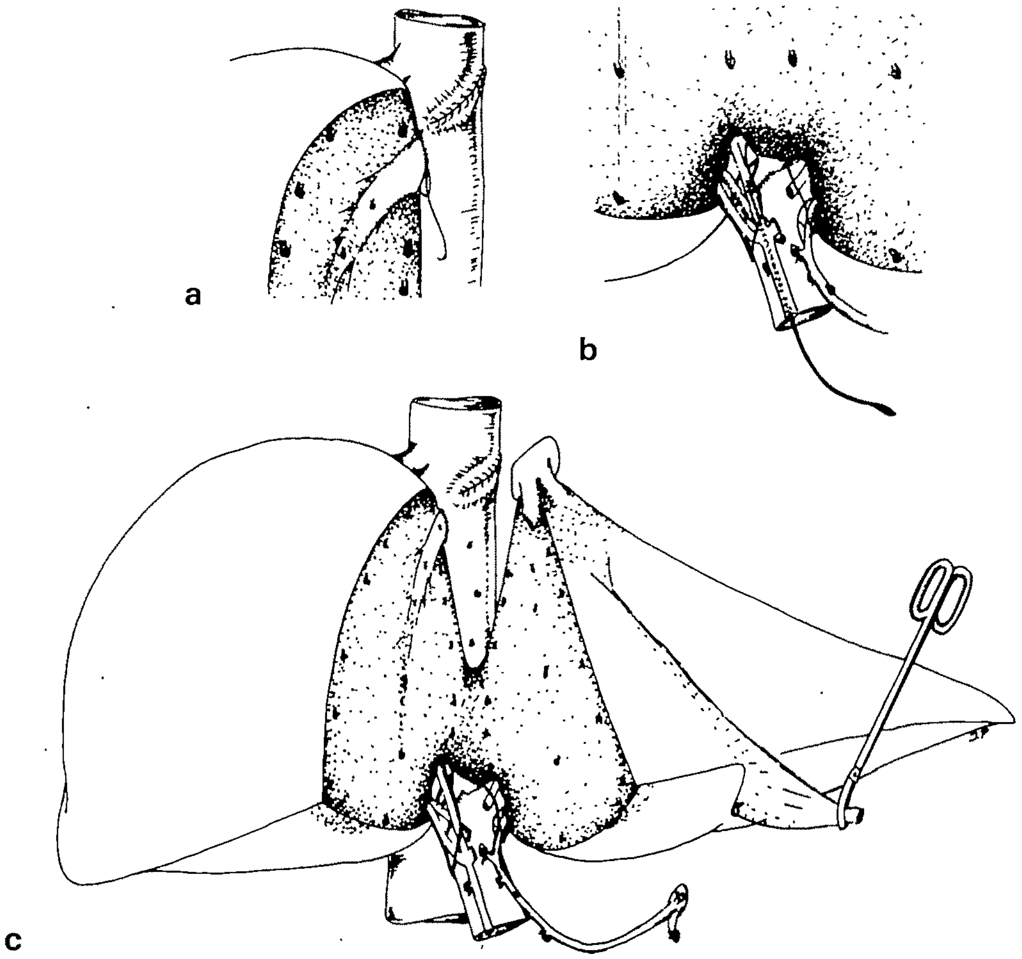

Figure 1 *Controlled liver splitting.* **a** *When a common trunk is found between left and middle hepatic veins, the middle hepatic vein, retained with the right graft, is anastomosed to the inferior vena cava, as in CLS7.* **b** *When cholangiography has shown a right biliary duplication, the bile duct is probed and the left hepatic duct divided, as in CLS2.* **c** *When arteriography has shown a unique left and right hepatic artery, the common hepatic artery is retained with the left graft to bridge the gap created by rotation of the graft to the right in the recipient, as in CLS2*

vein. The common trunk was retained with the left hepatic vein. The end of the middle hepatic vein was sutured in four cases (CLS1, CLS3, CLS5, CLS6), whereas in one (CLS7) it was anastomosed to the vena cava taken along with the graft after limited mobilization of the end of the middle hepatic vein from the surrounding parenchyma.

In the three other cases (CLS2, CLS4, CLS8) the ends of the middle and left hepatic veins were separate. Thus, on the right graft the middle hepatic vein was in continuity with the vena cava and the caval orifice of the left hepatic vein was sutured.

Step 3. In five cases (CLS1, CLS5, CLS6, CLS7, CLS8) a single duct was found on the right and left. Attribution of the short segment of common hepatic duct was by the surgeon's preference: to the right graft in three cases (CLS5, CLS7, CLS8) and to the left graft in two (CLS1, CLS6).

In three cases (CLS2, CLS3, CLS4) a duplication of the right bile duct was found. To avoid a double biliary anastomosis on the right graft, the end of the left hepatic duct was cut and the short segment of common hepatic duct retained with the right graft.

Division of the right or left bile duct was carried out after the parenchymal transection, without dissection into the liver hilum, the duct being located by a smooth probe before its section.

Step 4. In six cases a single middle hepatic artery was found. In five (CLS2, CLS5, CLS6, CLS7, CLS8) it had a single branch on the right and left; in four (CLS2, CLS5, CLS6, CLS8) the proper hepatic artery of the donor was retained with the left graft to bridge the distance from the stump of the recipient's hepatic artery. In one case (CLS7) the proper hepatic artery was allocated to the right graft to favour the recipient, who was undergoing transplantation electively. In the final case (CLS1) duplication of the left branch of the middle hepatic artery was found. The proper hepatic artery was retained with the left graft to avoid a precarious double arterial anastomosis on the left.

In two cases two hepatic arteries were found: in one (CLS3) a middle hepatic artery feeding the left liver, which was kept with the left graft, and a right hepatic artery coming from the superior mesenteric artery feeding the right liver, which was retained with the right graft; in the other (CLS4) a middle hepatic artery going to the right liver and segment IV was retained with the right graft, while a left hepatic artery coming from the left gastric artery, feeding the left lobe, was kept with the left graft.

Step 5. In four cases (CLS3, CLS5, CLS6, CLS8) segment IV was kept with the left graft. In the other four (CLS1, CLS2, CLS4, CLS7) resection of segment IV from the left graft was indicated because of the small size of the recipient. In no case was it necessary to remove segment IV from the left graft to solve the difficulty created by left arterial or biliary duplication with a distribution such that one branch is for segments II and III and the other for segment IV[11]. Segment I was always removed because of uncertainty regarding the origin of its portal veins and arteries and the end of its bile ducts.

Transplantation technique

In 14 cases the portal vein of the graft was anastomosed to the main portal vein of the recipient, in one (patient 6A) after thrombectomy of a portal vein thrombosis. In one case (patient 4B), because of an early arterial and portal vein thrombosis following a first liver graft and because of the very small calibre of the portal, superior mesenteric and splenic veins, the main portal vein taken with the left lobe graft was anastomosed end to end with the suprarenal inferior vena cava of the recipient. In another case (patient 6B) the main portal vein taken with the left graft was anastomosed to the right portal branch of the recipient.

In 14 cases the hepatic artery of the graft was anastomosed end to end to the hepatic artery of the recipient. In two cases an arterial graft was interposed between the hepatic artery of the graft and the hepatic artery (patient 5B) or infrarenal aorta (patient 3A) of the recipient.

In 13 cases the biliary reconstruction was to a Roux-en-Y jejunal loop. In three cases (patients 2B, 5B, 8B) the reconstruction was an end-to-end choledochocholedochal anastomosis with a T tube.

Anaesthesia, operative and cold ischaemia times

The mean anaesthesia time for both operations was 18 h 45 min (range 13–28 h). The mean operative time for both procedures was 16 h 30 min (range 11 h 45 min to 25 h 45 min). The mean cold ischaemia time was 12 h (range 6 h to 19 h 45 min) (*Table 2*).

Intraoperative haemorrhage after graft revascularization (Table 3)

The mean(s.d.) volume of red blood cells transfused during the postanhepatic phase was 45·8(60·8) (range 0–195·7) ml/kg.

In patients with a right graft the mean transfusion requirement was 69·6 (range 0–195·7) ml/kg. Bleeding was >100 ml/kg in two cases (patients 1B and 3B) in which the end of the middle hepatic vein of the graft had been sutured. This represented 65 and 82 per cent of the total intraoperative volume of transfusion, respectively, and was accompanied by congestion of the left and anterior side of segment V. In two other cases (patients 5B and 8B) bleeding was between 50 and 100 ml/kg. In one patient (5B), in whom the end of the middle hepatic vein of the graft had been sutured, bleeding was from the transected area, whereas in the other it was predominantly from the anastomotic sites. In the four other right grafts bleeding was moderate or absent. The middle hepatic vein was not interrupted in three and had been interrupted in one case (patient 6A), but in this liver it was small and received a large branch from segment IV.

In patients with a left graft the mean volume of red blood

Table 3 *Intraoperative bleeding during the postanhepatic phase, postoperative complications and graft and patient survival in 16 recipients of an allograft obtained by controlled liver splitting*

Patient no.	Red blood cell transfusion in postanhepatic phase (ml/kg)	Primary graft dysfunction	Hepatic artery thrombosis	Biliary complication	Reoperation*	Rejection	Retransplantation†	Patient outcome
1A	32·3	–	+ (day 3)	–	+ (arterial thrombectomy (1))	–	–	Alive and well
1B	189·4	–	–	–	–	–	–	Alive and well
2A	25·0	–	–	–	–	+ (severe, chronic)	–	Alive, awaiting regrafting
2B	9·1	–	–	–	–	–	–	Alive and well
3A	0	–	–	+	+ (reanastomosis for bile leak (1))	–	–	Alive and well
3B	195·7	+	–	+	+ (haematoma (1), reanastomosis for bile leak (2))	–	–	Alive and well
4A	15·8	–	+ (day 30)	+ (ischaemic cholangitis)	–	+ (moderate, acute)	+ (ischaemic cholangitis)	Alive and well
4B	33·3	–	+ (day 1)	–	–	–	+ (graft necrosis)	Died on day 5 (necrosis of third graft)
5A	15·0	–	–	–	–	+ (moderate, acute)	–	Alive and well
5B	52·3	–	–	–	+ (haematoma (1))	–	–	Alive and well
6A	17·4	–	–	–	–	+ (severe, acute)	–	Alive and well
6B	47·6	–	–	–	–	–	–	Died on day 23 (multiorgan failure)
7A	0	–	–	+ (anastomotic bile leak)	+ (abscess (2))	–	–	Alive and well
7B	7·8	–	–	–	–	–	–	Died on day 5 (brain haemorrhage)
8A	14·8	–	+ (day 29)	–	–	–	–	Alive and well
8B	77·4	–	–	–	–	–	–	Died on day 1 (brain death)

*Type of operation and number are given in parentheses; †indication in parentheses cells transfused during the postanhepatic phase was 21·9 (range 0–47·6) ml/kg.

Main postoperative surgical complications (Table 3)

Primary graft dysfunction was observed in one patient (3B). This liver had the longest cold ischaemia time and the heaviest bleeding after revascularization. Liver function improved from day 6 after operation. In the recipient of the corresponding left graft (patient 3A) postoperative recovery of liver function was normal.

Hepatic artery thrombosis was observed in four patients in this series (25 per cent). In the first case (patient 1A) thrombosis was diagnosed on day 3 by routine daily Doppler ultrasonography. An emergency reoperation was performed to remove the clot, to infuse urokinase into the hepatic artery and to refashion the anastomosis. Control intraoperative angiography showed patency of the small intrahepatic arterial branches. The subsequent course was uneventful. In the second case (patient 4A), because of a recent increase in the serum transaminase level with a normal Doppler signal, liver biopsy was carried out on day 28 after an injection of vasopressin. Histological examination showed moderate rejection. On the following day control Doppler ultrasonography suggested hepatic artery thrombosis, which was confirmed at angiography. Progressive ischaemic cholangitis led to retransplantation 3 months after the first transplantation.

In the third case (patient 4B) control Doppler ultrasonography showed recurrent thrombosis of the hepatic artery and portal vein anastomoses on day 1 which was confirmed by angiography. A third graft placed 2 days later was followed by early fatal thrombosis of the hepatic artery and portal vein. In the fourth patient (8A) a diminished arterial Doppler signal led to angiographic demonstration of stenosis of the arterial anastomosis. Because of severe neurological impairment, reoperation was not attempted. Despite heparin therapy, thrombosis occurred on day 29, confirmed by angiography. This patient remained asymptomatic. Neurological status improved and the child is now alive and well with normal biochemical liver test results.

One case of portal vein thrombosis (patient 4B) was reported above in association with hepatic artery thrombosis. In a second patient (6B) the postoperative course was dominated by bleeding from a gastric ulcer and progressive multiorgan failure. Whereas findings at previous examinations had been normal, premortem Doppler ultrasonography 22 days after grafting showed suspected thrombosis of the portal vein. Angiography was not carried out. The patient died a few hours later.

Biliary complications were observed in four patients (25 per cent) and required reoperation. An external bile leak followed by anastomotic stenosis (patient 3B) required refashioning of the hepaticojejunal anastomosis. Biliary peritonitis (patient 3A) required repeat choledochojejunal and jejunojejunal anastomoses. One patient with ischaemic cholangitis was described above. The fourth patient (7A) had a transient external biliary fistula (see below).

A haematoma on the cut surface of the liver required reoperation in two patients (3B and 5B) on days 10 and 14 respectively. Another patient (7A) underwent reoperations 11 and 22 days after grafting for an abscess related to a small biliary anastomotic leak which closed spontaneously.

Rejection, and patient and graft survival

Three patients had an acute rejection crisis. This was followed in one patient (2A) by the disappearance of small intrahepatic bile ducts.

The postoperative patient survival rate was 75 per cent. Four patients died: patient 4B died on day 5 from early recurrent thrombosis of the hepatic artery and portal vein of a third graft; patient 6B died on day 23 from multiorgan failure; patient 7B died on day 5 from brain haemorrhage; and patient 8B suffered brain death related to cerebral oedema a few hours after transplantation. The survival rate was 100 per cent in the four patients receiving non-urgent transplants and 67 per cent in the six who underwent transplantation for acute liver necrosis. The postoperative survival rate was also 67 per cent in the six patients in hospital or intensive care with end-stage chronic liver disease.

The immediate graft survival rate was 69 per cent (11 of 16); in addition to the four patients who died, one patient (4A) underwent retransplantation for ischaemic cholangitis. Another (2A) is awaiting retransplantation for chronic rejection.

Discussion

This study has shown that the technique of controlled liver splitting for transplantation in two recipients could be an acceptable method for increasing the number of liver allografts. This technique, which is based on all the major anatomical elements of the graft (size of the lobes; ends of hepatic veins; bifurcation of the portal vein; number, origins and destinations of bile ducts and hepatic arteries), includes cholangiography and arteriography on the back-table. Its safety relies in part on the precise recognition of anatomical variations and tailoring of the partition to them[11].

Portal vein bifurcation was present in all eight livers. Its absence is a rare anomaly, with a frequency of less than 1 per cent[11]; when present this would contraindicate the partition.

We suspect that, to avoid major bleeding from the raw surface of the right graft, the patency of the middle hepatic vein, which is kept with it, must be ensured. Probably because of anastomotic veins between right and middle hepatic veins[13–16], surgical ligation of such a main vein is well tolerated[17,18]. However, the increased venous pressure can be a source of major bleeding. Thus, in the present series, bleeding from the transected surface of the right graft appeared greater when the middle hepatic vein kept with the graft had been ligated at its end. This risk is probably significant when the middle hepatic vein drains a large territory of the right liver, which occurs in 36 per cent of cases[19]. For this reason, when there is a common trunk of the left and middle hepatic veins which requires section of the end of the middle hepatic vein, this end should be implanted directly or indirectly into the vena cava.

Without dissection of the liver hilum, three right biliary duplications were detected. This is the commonest biliary variation and occurs in 44 per cent of cases[11]. Dissection carries a risk of injury to the thin vascular sheath of the bile duct wall, with subsequent risk of ischaemia. To avoid such dissection, cholangiography is required to detect duplication of the right main duct. In these cases the residual common duct is retained with the right liver to avoid a double biliary anastomosis with its additional risk.

Duplication of the left branch of the middle hepatic artery, as found in one of the present cases, is observed in approximately 26 per cent of livers. In this case (CLS1), because of its small calibre, the duplicated artery supplying segment II could easily have been cut during dissection, leading to ischaemia of a part of the liver graft or requiring an additional precarious microanastomosis. Arteriography of the graft is essential to identify such variations.

In this short series, the high incidence of hepatic artery thrombosis raises the possibility that arteriography on the back-table is a predisposing factor. It could be argued in one case (patient 4A) that thrombosis was probably caused by injection of vasopressin and in another (4B) that some unrecognized thrombotic factor may have been involved since, in this child, all six attempts at ensuring portal or arterial blood flow to the liver graft failed. However, we suspect that injecting a potentially irritating contrast medium into the artery may have played a role even though it was thoroughly washed out immediately after opacification. Nevertheless, the use of a more dilute solution or a less irritating neuroradiological contrast medium might be preferable[20]. The small calibre of the hepatic artery on one of the two grafts could be another reason for the thrombosis, but two of the four thromboses occurred with left grafts on which the proper hepatic artery had been kept and which therefore did not differ in this respect from a reduced-size hepatic graft, in which the rate of hepatic artery thrombosis is 5 per cent in the experience of the present authors[6].

The disappointing results initially reported with split liver transplantation[7–9,21,22] led Broelsch *et al.* to conclude that this technique is not safe enough to be pursued and to look for other methods to improve the feasibility of transplantation[10]. When analysed according to the preoperative status of the patients, the present results appear more encouraging. In spite of prolonged ischaemia time, primary non-function of a graft was not observed. Necrosis of segment IV[8,9] was avoided by a policy never to keep this segment with the right graft.

Controlled liver splitting for transplantation in two recipients causes logistical problems for the medical institution. To minimize night-time work and limit the cold ischaemia time to <20 h, simultaneous access to two operating theatres and participation of two anaesthetic and surgical teams are essential.

Controlled liver splitting for transplantation in two recipients also raises new ethical problems, similar to those raised by the conflict between individual medical benefit and the rational management of limited resources. If there is a risk related to controlled liver splitting, should it be shared between the two recipients or should one recipient be favoured and, if so, which? It was felt that the first option was preferable. Use of the second liver graft would be unethical if this graft was always deprived of the main portal vein, the proper hepatic artery and the remaining segment of the common bile duct, whatever the anatomical situation. For this purpose, if one of the two grafts is to be sent to another transplant centre, early and close links between donor and recipient teams should enable the inclusion of such recipient-specific factors as body-weight and patency of the portal vein in the decision concerning the exact technique of splitting. Even if it is desirable[23], allocation of the liver graft generated by partition of the donor liver strictly according to the guidelines of the network for organ sharing is not yet possible. However, in the same way as retrieval of the liver has been progressively expanded to centres in which donor operations were limited to kidney removal, sharing a liver between two recipients may in the future be imposed by the shortage of grafts. For all these reasons, it seems that precise technical guidelines for the performance of liver splitting for transplantation in two recipients are invaluable.

References

1. Bismuth H, Houssin D. Reduced size orthotopic liver grafts in hepatic transplantation in children. *Surgery* 1984; **95**: 367–70.
2. Strong R, Ong TH, Pillay P, Wall D, Balderson G, Lynch S. A new method of segmental orthotopic liver transplantation in children. *Surgery* 1988; **104**: 104–7.
3. Ringe B, Pichlmayr R, Burdelski M. A new method of hepatic vein reconstruction in partial liver transplantation. *Transplant Int* 1988; **1**: 30–5.
4. Otte JB, de Ville de Goyet J, Sokal E *et al.* Size reduction of the donor liver is a safe way to alleviate the shortage of size-matched organs in pediatric liver transplantation. *Ann Surg* 1990; **211**: 146–57.
5. Broelsch CE, Emond JC, Thistlethwaite JR *et al.* Liver transplantation including the concept of reduced-size liver transplants in children. *Ann Surg* 1988; **208**: 410–20.
6. Houssin D, Soubrane O, Boillot O *et al.* Orthotopic liver transplantation using a reduced-size graft: an ideal compromise in pediatrics? *Surgery* 1992; **111**: 532–42.
7. Pichlmayr R, Ringe B, Gubernatis G, Hauss J, Bunzendahl H. Transplantation einer Spenderleber auf bei zwei Empfänger (splitting-transplantation). Eine neue Method in der Weiterentwicklung der Lebersegmenttransplantation. *Langenbecks Arch Chir* 1988; **373**: 127–30.
8. Emond JC, Whitington PF, Thistlethwaite JR *et al.* Transplantation of two patients with one liver. Analysis of a preliminary experience with 'split-liver' grafting. *Ann Surg* 1990; **212**: 14–22.
9. Broelsch CE, Emond JC, Whitington PF, Thistlethwaite JR, Baker AL, Lichtor JL. Application of reduced-size liver transplants as split grafts, auxiliary orthotopic grafts, and living related segmental transplants. *Ann Surg* 1990; **212**: 368–77.
10. Broelsch CE, Whitington PF, Emond JC *et al.* Liver transplantation in children from living related donors. Surgical techniques and results. *Ann Surg* 1991; **214**: 428–39.
11. Couinaud C, Houssin D. *Controlled Partition of the Liver for Transplantation. Anatomical Limitations.* Paris: C. Couinaud and D. Houssin pers. ed., 1991: 1–80.
12. Houssin D, Couinaud C, Boillot O *et al.* Controlled hepatic bipartition for transplantation in children. *Br J Surg* 1991; **78**: 802–4.
13. Elias H, Petty D. Gross anatomy of the blood vessels and biliary ducts within the human liver. *American Journal of Anatomy* 1952; **90**: 59–111.
14. Couinaud C, Nogueira C. Les veines sus-hépatiques chez l'homme. *Acta Anat (Basel)* 1958; **34**: 84–110.
15. Lasinski W, Zientarski B. Contribution à l'étude du système anastomotique des veines sus-hépatiques chez l'homme. *Bull Assoc Anat (Nancy)* 1976; **60**: 559–66.
16. Masselot R, Leborgne J. Etude anatomique des veines sus-hépatiques. *Anatomica Clinica* 1978; **1**: 109–25.
17. Quing Jia O, Hermann RE. The role of hepatic veins in liver operations. *Arch Surg* 1980; **121**: 515–21.
18. Quing Jia O, Xiujing Z, Moye C, Tianki H. A new concept concerning the role of hepatic vein in liver surgery (experimental studies for the possibility of preserving the hepatic segment after hepatic vein ligation). *Acta Academica Medica Zhong Shan* 1983; **4**: 39–47.
19. Couinaud C, Houssin D. Bipartage réglé du foie en vue de transplantation. Simplification de la méthode. *Chirurgie* 1992 (in press).
20. Bettman MA. Radiographic contrast agents: a perspective. *N Engl J Med* 1987; **317**: 891–3.
21. Bismuth H, Morino M, Castaing D *et al.* Emergency orthotopic liver transplantation in two patients using one donor liver. *Br J Surg* 1989; **76**: 722–4.
22. Otte JB, de Ville de Goyet J, Alberti D, Balladur P, de Hemptinne B. The concept and technique of the split liver in clinical transplantation. *Surgery* 1990; **107**: 605–12.
23. Merion RM, Campbell DA. Split-liver transplantation: one plus one doesn't always equal two. *Hepatology* 1991; **14**: 572–4.

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Liver transplantation in patients with thrombosis of the portal, splenic or superior mesenteric vein

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Fourteen cases are presented of preoperative portal vein thrombosis complicating orthotopic liver transplantation from an experience of 195 transplants carried out between April 1986 and April 1991. In four patients who suffered rethrombosis of the portal vein, the mortality rate was 100 per cent from various causes. Overall there were six deaths; two of those who died had a patent portal vein at death. Three patients underwent retransplantation: one for primary non-function, two for rejection. It is concluded that: (1) portal vein thrombosis should not represent an absolute contraindication to liver transplantation; (2) preoperative screening of prospective transplant recipients for portal thrombosis should be routine; (3) postoperative anticoagulation therapy and periodic Doppler ultrasonographic assessment of portal vein flow are important elements of post-transplant management; and (4) with thrombectomy and portal vein resection an end-to-end portal anastomosis may be performed with good results.

Portal vein thrombosis (PVT) may occur as a cause[1,2] or consequence of portal hypertension as a result of slowed blood flow, increased hepatic resistance or the presence of a hepatocellular tumour at the hepatic hilum[3–6].

Recurrence of PVT after transplantation occurs as a result of poor surgical technique (kinking or stretching of the vessels) which can result in decreased blood flow[7,8], or secondarily to microbial infection and, less frequently, immunosuppressive therapy[9].

PVT constituted an absolute contraindication to orthotopic liver transplantation (OLT)[10] until success was reported with thrombectomy or anastomosis between the donor portal vein and the recipient superior mesenteric[11,12] or left gastric[13] vein.

At this institution, evidence of PVT has never been a contraindication to OLT, first because techniques are now available to restore portal flow and perfuse the graft (removal of thrombus, resection of the portal vein, venous graft) and second because OLT constitutes the only valid therapeutic option that can be offered to those severely ill patients who would otherwise die within a short period of time. PVT was present in 14 of 174 patients undergoing OLT between April 1986 and April 1991.

Although it is already known that OLT is feasible in patients with PVT, the aim of this study was to confirm that the operation is beneficial in these circumstances.

Patients and methods

Of 195 OLTs performed in 174 patients at this institution, in 14 there was preoperative PVT. Diagnosis was reached by Doppler ultrasonography in five cases and confirmed by splenoportal arteriography and superior mesenteric venography. In the remaining nine patients, preoperative studies undertaken when the recipients were entered on to the waiting list for OLT had indicated normal flow and diameter of the portal, splenic and superior mesenteric veins, but PVT was found at laparotomy 2–3·5 months later.

Eleven patients were male and ages ranged from 36 to 60 years. The indication for transplantation was alcoholic cirrhosis in six patients, cryptogenic cirrhosis in five, primary biliary cirrhosis in one, posthepatitis B virus cirrhosis in one and autoimmune cirrhosis in one. Ten patients suffered ascites, estimated at 4–16 litres. Malnutrition was present in eight patients, jaundice in seven and severe bleeding diathesis (prothrombin activity <40 per cent, fibrinogen level <150 mg/dl and platelet count $<70 \times 10^9$/l) in 11. All patients were classified as Child's grade C.

The patients had suffered from two to six haemorrhagic episodes, treated in all cases by endoscopic sclerotherapy (from two to five sessions of intravenous and perivenous sclerotherapy). Nine patients had had episodes of encephalopathy, with signs that this was chronic in five. One patient with alcoholic cirrhosis (no. 8) was positive for hepatitis B virus surface antigen.

The waiting period between diagnosis and transplantation varied from 2 weeks to 4 months 2 days (mean 3 months 20 days). Hospital admissions during this waiting period included four patients with gastrointestinal haemorrhage, two with encephalopathy and three with ascites. Seven patients suffered chronic renal insufficiency but none required dialysis.

The protocol for post-transplant care included repeated study of vascular patency by Doppler ultrasonography; this was also performed when laboratory parameters of hepatic function were sufficiently altered. Only when ultrasonography gave inconclusive results (patient 12) or could not be performed (patient 5) was arteriography carried out to evaluate portal patency in the venous phase. Previous experience[14] has shown that the final diagnosis of vascular patency is the same using Doppler ultrasonography and arteriography, which has been replaced by the former in this institution.

The surgical approach was by bilateral subcostal laparotomy in two patients and an oblique incision with a central extension in the supraumbilical midline in the remaining 12.

Severe portal vein hypertension was evident in all patients, with abundant dilated venous collaterals in the hepatoduodenal ligament, especially over the surface of the common and accessory bile ducts. After division of the branches of the hepatic artery and the common hepatic duct distal to the confluence of the hepatic ducts, the presence of PVT was confirmed by dissection of the portal vein to the confluence of the splenic, superior mesenteric and coronary gastric veins.

Total obstruction of the portal vein was found in 11 patients, 75 per cent occlusion in one and 50 per cent occlusion in the remaining two (*Table 1*).

The portal vein was cut proximal to its bifurcation in all patients, providing further confirmation of PVT, with minimal bleeding in the three patients with partial obstruction and none in the 11 with total occlusion.

Thrombectomy was performed in 13 patients, to remove the occluding thrombus (always white and organized) from the portal vein. A completely occlusive thrombus had extended into the splenic vein alone in three patients and into both the splenic and superior mesenteric veins in two; it was extracted in two to four pieces in five patients and in multiple fragments in the other eight. Retrograde dilatation was necessary using a gallstone forceps or Fogarty catheter in all patients, followed by introduction of heparinized saline solution, which was retained for several minutes. These procedures were repeated if necessary until good blood flow was obtained from the portal vein; a cell saver was used during operation in one case. One patient (no. 12)

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Table 1 *Operative details of patients with portal vein thrombosis and current status of the portal vein*

Patient no.	Transplant no.	Extent of thrombosis*	Extracorporeal venous bypass	Preserving solution	Venous anastomosis	Portal status
1	43	PV (SV–SMV)	Yes	Collins	PV–SV, PV	Thrombosed
2	51	PV–SV	Yes	Collins	PV–LGV	Thrombosed
3	66, 73, 74	PV–SV–SMV	Yes	Collins	PV–SV, SMV	Patent
4	87	PV–(SMV)	Yes	Collins	PV–SV, LGV	Patent
5	94	PV (SMV)	Yes	Collins	PV–PV	Thrombosed
6	102, 103	PV–SV	Yes	Collins	PV–SV, SMV	Patent
7	116, 138	(PV) (50%)	No	Belzer	PV–PV	Patent
8	119	(PV) (75%)	No	Belzer	PV–PV, SMV	Patent
9	120	PV–SV	No	Belzer	PV–PV, SMV	Patent
10	121	PV–(SMV)	No	Belzer	PV–PV	Patent
11	132	PV–(SV–SMV)	No	Belzer	PV–SMV–SV	Patent
12	151	PV–SV–SMV	No	Belzer	PV–SMV† (internal jugular vein graft)	Thrombosed
13	161	PV (SV–SMV)	No	Belzer	PV–SV, SMV	Patent
14	169	(PV) (50%)	No	Belzer	PV–PV	Patent

PV, portal vein; SV, splenic vein; SMV, superior mesenteric vein; LGV, left gastric vein. *Parentheses indicate partial occlusion; †patient remained comatose after operation but retained good hepatic function – autopsy 3·5 months after transplant revealed portal vein thrombosis

had complete thrombosis of the portal, splenic and superior mesenteric veins.

The donor liver was perfused with Hartmann's solution (precooling) and Collins' solution (cooling) in six patients. In eight cases, Belzer's solution was perfused through the portal vein (1·5–2 litres) and the abdominal aorta (1·5–2 litres) (*Table 1*).

Extracorporeal venovenous bypass (portal–femoral–axillary circuit) was used in six patients. No bypass was used in the last eight patients after introduction of a new surgical protocol, established after transplant no. 104, which called for the use of bypass only if serious haemodynamic changes resulted from vascular clamping of the portal vein and hepatic artery.

The portal vein was resected to the level of the left coronary vein in 11 patients; this resection was extended to the union of the splenic and superior mesenteric veins in two. In the remaining patient the portal vein had been transformed into a fibrous cord in which it was impossible to re-establish a lumen. For this reason, after division of the splenic and infrapancreatic superior mesenteric veins to confirm obstruction, the venous trunk was further dissected to the confluence of the first jejunal veins and the ileocolic vein. The vein was divided at this point and anastomosis performed between this confluence and a left internal jugular vein graft, the proximal end of which was anastomosed to the portal vein of the liver graft.

From the descriptions above, the extent of PVT may be classified as: (1) partial (three patients – 50 per cent in two, 75 per cent in one); (2) total, with laminar thrombosis of the superior mesenteric vein (three patients); (3) total, associated with partial splenic and superior mesenteric vein thrombosis (three patients); (4) total, associated with total splenic and superior mesenteric vein thrombosis (one patient); (5) total, associated with total splenic vein thrombosis (three patients); and (6) total thrombosis of the portal, superior mesenteric and splenic veins with extension to the trunk of the jejunal and ileocolic veins (one patient) (*Table 1*).

Results

Tolerance of infrahepatic vein clamping

Occlusion of the inferior vena cava before removal of the recipient liver reduced the arterial pressure by 20–40 (mean 27·0) mmHg and the central venous pressure by 3–6 (mean 4·2) mmHg. Both parameters returned to nearly normal levels after rapid blood transfusion.

Perioperative blood loss

Blood loss during operation was estimated to be from 3 to 17 (mean 7·5, median 5) units. Very small differences were found between patients treated during the anhepatic phase with or without portofemoroaxillary bypass. Using bypass the blood loss increased (mean 9·0, median 8 units).

Patency of the portal anastomosis

Four patients were found to have PVT between 7 days and 2 months after OLT. In one (patient 5), PVT had been suspected from an abrupt rise in the level of bilirubin and transaminases, and deterioration of coagulation factors on day 5 after operation; because Doppler ultrasonography could not be performed, portal venography and hepatic arteriography were used to show vessel patency. However, 24 h later laboratory parameters revealed severe deterioration and the patient died in liver failure shortly afterwards, awaiting retransplantation. Autopsy revealed the existence of an extensive red thrombus in the portal vein and superior mesenteric vein and its branches.

The patient who received the jugular vein graft between the portal vein of the liver graft and the jejunal and ileocolic veins (patient 12) showed reduced blood flow on ultrasonography 1 month after transplant; arteriography revealed a significant reduction in flow consistent with laminar thrombosis. Autopsy findings more than 2 months after transplant confirmed the presence of extensive portal and mesenteric thrombosis.

In the remaining ten patients, portal vein patency was confirmed by various ultrasonographic studies throughout the postoperative course.

Laboratory parameters of hepatic function

Only two of four patients with postoperative PVT demonstrated laboratory abnormalities a short time before the thrombosis was shown (nos 2 and 5). In patient 2, there was no doubt about the relationship between PVT and hepatic necrosis, as shown by raised levels of hepatic transaminases (*Figure 1*), because PVT was the only final diagnosis and hepatic arterial flow was normal. This relationship was less clear in patient 5, in whom digital angiography showed continued portal vein patency 2 days after the rise in concentration of liver enzymes (*Figure 2*). However, the patient died 1 day after angiography, awaiting retransplantation, and autopsy revealed massive necrosis of the liver with complete PVT.

In the remaining patients, changes in parameters of hepatic function occurred in relation to episodes of acute and chronic rejection diagnosed by percutaneous biopsy of the graft.

Graft rejection

Only one of four patients with thrombosis of the portal anastomosis (patient 1) suffered episodes of acute (on day 10 after operation) or chronic (6 months after transplant)

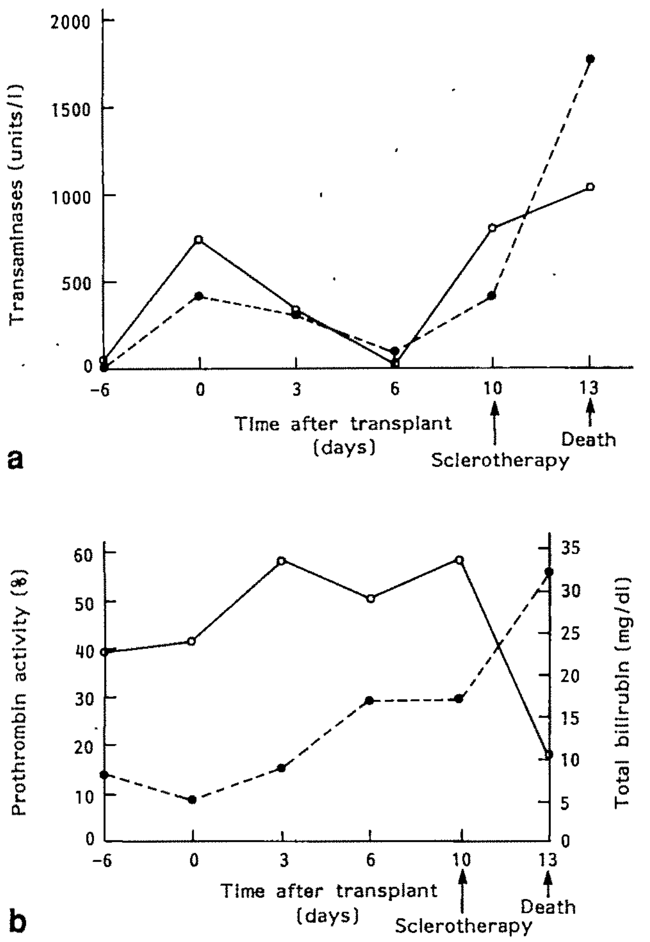

Figure 1 *Changes of biochemical parameters in patient 2.* **a** ○, *Serum glutamic-oxaloacetic transaminase;* ●, *serum glutamic-pyruvic transaminase.* **b** ○, *Prothrombin activity;* ●, *bilirubin*

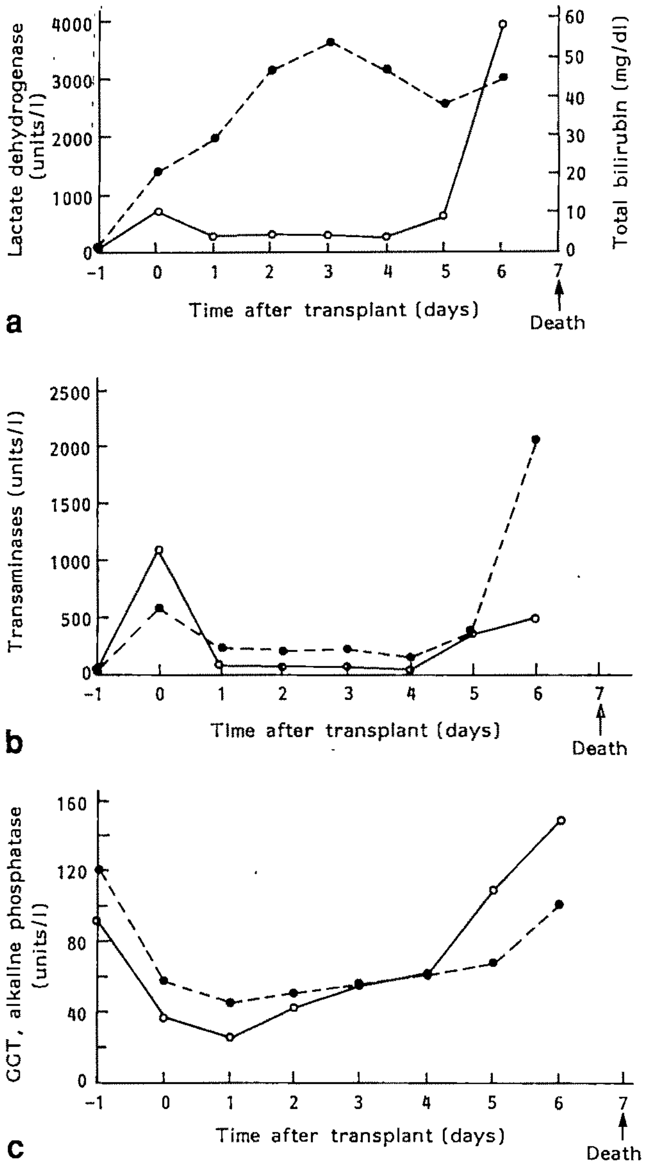

Figure 2 *Changes of biochemical parameters in patient 5.* **a** ○, *Lactate dehydrogenase;* ●, *bilirubin.* **b** ○, *Serum glutamic-oxaloacetic transaminase;* ●, *serum glutamic-pyruvic transaminase.* **c** ○, *γ-Glutamyl transferase (GGT);* ●, *alkaline phosphatase*

rejection. The chronic rejection did not respond completely to immunosuppressive treatment with monoclonal antibodies and resulted in the patient's death 2 months later.

Arterial thrombosis

Two patients suffered postoperative hepatic arterial thrombosis. One case (patient 2) was likely to have been caused by the administration of somatostatin given to treat an episode of bleeding oesophageal varices, since the arterial thrombosis followed 24 h later. In the other patient (no. 3), thrombosis appeared to be due to acute rejection occurring 38 days after transplant, since there was no evidence of other causes and because previous experience of nine cases of arterial thrombosis[14] had shown that eight were related to severe acute rejection, suggesting that reduction of the donor arterial lumen and increased resistance to blood flow were the main causes. Endoluminal angioplasty was not attempted in any of these patients because of severe deterioration of coagulation.

The association of arterial thrombosis with pre-existing PVT (patient 2) resulted in autopsy findings of total necrosis of the liver graft.

Retransplantation

Retransplantation was not suggested in any patient for isolated PVT.

Three patients underwent retransplantation. In one (patient 3) this was due to deterioration of hepatic function following arterial thrombosis; retransplantation was performed 45 days after the original OLT, but the new graft suffered primary failure and 5 days later the patient underwent a second retransplantation. Death ensued 12 days later from sepsis, pulmonary aspergillosis and multiorgan failure.

Patient 6 underwent retransplantation for primary graft failure 5 days after transplant, but died 14 days later from pulmonary aspergillosis leading to sepsis and multiorgan failure.

Patient 7 suffered chronic rejection and underwent retransplantation 3·5 months after the original OLT. The patient suffered episodes of rejection of the new graft as well as bacterial infection, both of which were controlled.

Patients 1 (acute rejection), 2 (recurrence of PVT) and 5 (acute rejection) all had indications for retransplantation but died awaiting another donor liver (*Table 2*).

Mortality

Three patients died during the 30-day postoperative period, from PVT with digestive haemorrhage and associated arterial thrombosis (patient 2), acute rejection followed by multiorgan failure and PVT (patient 5) and multiorgan failure with pulmonary aspergillosis without evidence of PVT (patient 6) (*Table 2*).

Three patients died during the follow-up period. One patient (no. 1) died from chronic rejection 8·5 months after transplant

Table 2 *Aetiology of cirrhosis, complications of transplantation and outcome*

Patient no.	Aetiology of cirrhosis	Date of first OLT	Duration of follow-up	Complications	Date of second OLT	Outcome
1	Biliary	6 June 1988	8 months 10 days	Acute rejection	—	Chronic rejection; died
2	Autoimmune	19 July 1988	13 days	Rethrombosis Gastrointestinal bleed	—	Arterial thrombosis; died
3	Cryptogenic	2 December 1988	1 month 25 days	Acute rejection	17 January 1989* (primary non-function)	Sepsis, aspergillosis, multiorgan failure; died
4	Alcoholic	25 June 1989	2 years	Rejection (4 times)	—	Well
5	Cryptogenic	7 September 1989	8 days	Acute rejection Hepatic failure	—	Rethrombosis, multiorgan failure; died
6	Cryptogenic	1 November 1989	19 days	Primary non-function	6 November 1989	Multiorgan failure, aspergillosis; died
7	Cryptogenic	12 March 1990	1 year 2 months	Chronic rejection	26 June 1990	Well
8	Alcoholic	31 March 1990	1 year 2 months	Acute rejection	—	Well
9	Alcoholic	3 April 1990	1 year 1 month	Cholestasis	—	Well
10	Alcoholic	6 April 1990	1 year 1 month	—	—	Well
11	Cryptogenic	30 May 1990	1 year	Cholestasis Cholangitis	—	Well
12	Alcoholic	28 August 1990	2 months	Cerebral ischaemia	—	Good hepatic function; died
13	Alcoholic	28 October 1990	7 months	—	—	Well
14	Posthepatitis	12 December 1990	5 months	—	—	Well

OLT, orthotopic liver transplantation. *Patient underwent third OLT on 22 January 1989

while awaiting retransplantation, from rapid multiorgan deterioration.

One patient (no. 3) died after second and third transplants 2 months after the original OLT from sepsis, aspergillosis and multiorgan failure.

The third patient (no. 12) died from pulmonary infection 4·5 months after transplant. This patient had suffered an episode of cerebral ischaemia 36 h after transplantation that had caused diffuse irreversible brain damage and necessitated tracheostomy and assisted ventilation (*Table 2*).

Survival

Eleven patients survived for between 2 months and 2 years after transplant, and of these eight are currently alive and without complications; they maintain normal hepatic function. Portal vein and hepatic arterial patency have been confirmed in all 11 patients (*Table 2*).

Relationship between preservation solution, venovenous bypass and results

In six patients perfusion and preservation of the liver graft was carried out with Hartmann's (precooling) and Collins' (cooling) solutions; venovenous bypass was used in all six. In contrast, in the eight remaining cases, perfusion was performed with Belzer's solution and venovenous bypass not employed.

Five patients in the first group died, while in the second there was one death. Similarly, PVT recurred in three patients in the first group and in one of the second. Two patients underwent retransplantation in the first group and one in the second. The χ^2 test with Yates' correction revealed no significant differences between groups with respect to these three parameters.

Discussion

The demonstration of PVT in terminal hepatic cirrhosis represents for some an absolute contraindication to OLT[10,11] since the severe portal hypertension can complicate the surgical procedure. Depending on the extent of thrombosis it is also necessary to resect the portal vein or construct different bypasses (usually with an iliac vein graft of the donor) to allow venous perfusion of the graft by way of the superior mesenteric or left gastric vein[12]. However, the major risk of accepting these patients for OLT is the recurrence of PVT after operation due to the involvement of the vessel wall of the portal or splenic and superior mesenteric veins and the reduction in portal venous flow caused by the extensive collateral circulation developed as a result of portal thrombosis[12,13,15].

Partial thrombosis of the portal vein is common, although minor reductions (<25 per cent) of the portal lumen are not clinically significant. However, thrombectomy and resection of the major part of the involved venous wall should be performed when the reduction of the venous lumen is >25 per cent. Reductions of <25 per cent are localized and can be treated by resection of the portal vein.

The presence of left gastric vein dilatation necessitates ligation of this vessel to avoid the loss of portal vein blood and to facilitate the increase of portal vein diameter by longitudinal incision of the vessel wall, which improves the anastomosis with the donor portal vein. Alternatively, the left gastric vein may be used to create an anastomosis with the portal vein of the graft[13].

Venovenous bypass was used in this series only between the femoral and axillary veins. This blood flow is similar to that which exists in the portal–femoral–axillary circuit from the extensive collateral circulation between the splanchnic and general circulation. For precisely this reason, clamping of the infrahepatic vena cava is well tolerated by these patients and the use of venovenous bypass not necessary. In the present study, at least, an apparently lower incidence of recurrent thrombosis was achieved in the patients in whom bypass was not used; a similar improvement in results was apparent in those patients who received liver grafts perfused with Belzer's solution, although in both cases the numbers are too small for statistical confirmation. Perhaps the combination of avoiding trauma to the vessel during the hypercoagulable phase following bypass and the improved preservation (including decreased damage to the vascular endothelium) contributed to this improvement in results[14,16]. This idea is supported by the fact that there have been no cases of arterial thrombosis and only one of vein thrombosis (in a patient with preoperative PVT) in the last consecutive 92 OLTs in which Belzer's solution was used and venous bypass not applied.

Postoperative mortality was not clearly related to complications secondary to the recurrence of PVT; the incidence was high in the first group (perfusion with Hartmann's and Collins' solutions and use of venous bypass) and low in the second (perfusion with Belzer's solution and no bypass). For this reason, although the influence of these factors on postoperative outcome is debatable, we intend to continue with the latter protocol[14].

The 3-month and long-term survival rates do not appear to differ from the overall mean observed in the European Liver Transplant Registry. However, survival in the present patients is significantly worse than that achieved by the most experienced groups in the Registry at 1 and 3 years after transplantation[17].

Recurrence of PVT in the present series could be related to the coagulative state. In the first five patients, anticoagulation was not carried out because it was not considered necessary due to the low coagulative state in the early postoperative period. In the last nine patients anticoagulation was maintained for 2–3 months. Anticoagulation therapy during the first 3–6 months after OLT should be administered in a carefully controlled manner, with prothrombin activity maintained at ≤50 per cent and cephalin time within 40 per cent of control values[11,18].

PVT should not be a contraindication to OLT[19,20] although it does currently necessitate a more complex surgical reconstruction and may also raise the overall morbidity and mortality rates of transplantation. In any case it should be remembered that PVT can occur during the waiting time in the pretransplant period after normal ultrasonographic studies have indicated portal vein patency, and thus may be present as an unexpected operative finding[12–14]. Although the patients in the present study constituted the worst candidates for OLT, we consider that the high risk of an H graft mesocaval shunt and the contraindication of a distal splenorenal shunt (because of intractable ascites) mean that OLT is the only option that can be offered to such patients. On the other hand, portosystemic shunting before transplantation increases morbidity and mortality and also the risk of PVT in the recipient[21,22]. The only indication for a pretransplant shunt is failure of sclerotherapy as treatment for bleeding oesophageal varices.

The recurrence of PVT after operation is not always associated with changes in hepatocellular activity, as demonstrated by the course of two of the present patients. However, in those cases in which evidence of progressive hepatic atrophy exists[19,20], hepatic function may be preserved and catastrophic haemorrhage avoided by an operative portosystemic shunt procedure[21,22]. Of these the distal selective splenorenal shunt is preferred since this region is located away from the hepatoduodenal ligament, which facilitates the procedure. However, it is still not clear whether there can be any indication for a shunt in such patients, or whether sclerotherapy should be the treatment of choice.

The incidence of postoperative PVT was not underestimated because Doppler ultrasonography constitutes a good diagnostic method in this department[14]. If PVT does not occur in the early postoperative period it seems unlikely to develop during follow-up. In the experience of the authors postoperative PVT has never occurred in patients with a patent portal vein (follow-up from 2 months to 2 years; 174 patients until April 1991), unless severe complications (acute pancreatitis, multiorgan failure) have appeared.

In conclusion, OLT has been found to be a satisfactory treatment for patients with end-stage liver failure and PVT. The present results, particularly if venous bypass is not used and the donor liver is perfused with Belzer's solution, are similar to those obtained after liver transplantation without PVT.

References

1. O'Donnell B, Moloney MA. Development and course of extrahepatic obstruction in children. *Lancet* 1968; **i**: 789–91.
2. Alvarez F, Bernhard O, Brunell F. Portal obstruction in children. II. Results of portosystemic shunts. *J Pediatr* 1983; **103**: 703–7.
3. Hunt AM, Whittard BR. Thrombosis of the portal vein in cirrhosis hepatitis. *Lancet* 1954; **i**: 281–4.
4. Laws JW, Leith R, Steiner RE. Extrahepatic portal vein obstruction. *Br J Radiol* 1959; **32**: 774–90.
5. Maddrey WC, Basu Malic KC, Iber FL, Basu AK. Extrahepatic obstruction of the portal venous system. *Surg Gynecol Obstet* 1968; **127**: 989–98.
6. Okuda K, Ohnishi K, Kimura K *et al*. Incidence of portal vein thrombosis in liver cirrhosis. An angiographic study in 708 patients. *Gastroenterology* 1985; **2**: 279–86.
7. Yanaga K, Shimada M, Makowka L, Esquivel CO, Tzakis AG, Starzl TE. Significance of blood flow measurement in clinical liver transplantation. *Transplant Proc* 1989; **1**: 2330–1.
8. Lerut J, Tzakis AG, Bron K *et al*. Complications of venous reconstruction in human orthotopic liver transplantation. *Ann Surg* 1987; **215**: 404–14.
9. Weitz H, Goke JM, Loeschke K, Possinger K, Eder M. Veno-occlusive disease of the liver in patients receiving immunosuppression therapy. *Virchows Arch A Pathol Anat Histopathol* 1982; **395**: 245–56.
10. Van Thiel DH, Schade RR, Gavaler JS, Shaw BW, Iwatsuki S, Starzl TE. Medical aspects of liver transplantation. *Hepatology* 1984; **4**: 795.
11. Helling TS. Thrombosis and recanalization of the portal vein in liver transplantation. *Transplantation* 1985; **40**: 446–8.
12. Starzl TE, Todo S, Tzakis AG *et al*. Liver transplantation: an unfinished product. *Transplant Proc* 1989; **1**: 2197–200.
13. Czernia KA, Badger I, Sherlock D, Buckels J. Orthotopic liver transplantation in a patient with thrombosis of the hepatic portal and superior mesenteric veins. *Transplantation* 1990; **2**: 334–5.
14. Moreno González E, García García I, Gómez Sanz R, González-Pinto I, Loinaz Segurola C. Trasplante hepático ortotópico. Nuestra experiencia. *Rev Esp Enferm Dig* 1990; **5**: 295–302.
15. Warren WD, Milliken WJ, Smith RB. Noncirrhotic portal vein thrombosis. *Ann Surg* 1980; **190**: 341–8.
16. Belzer FO, Southard JH. Principles of solid organ preservation by cold storage. *Transplantation* 1988; **45**: 671–3.
17. European Liver Transplant Registry. *Collection of Data 6*. 1990.
18. Perry MO. Anticoagulation: a surgical perspective. *Am J Surg* 1988; **155**: 268–71.
19. Schalm L, Bax HR, Mansens BJ. Atrophy of the liver after occlusion of the bile ducts or portal vein and compensatory hypertrophy of the unoccluded portion and its clinical importance. *Gastroenterology* 1956; **31**: 131–5.
20. Starzl TE, Francavilla H, Galgrimson CG. The origin, hormonal nature, and action of hepatotrophic substances in portal blood. *Surg Gynecol Obstet* 1975; **137**: 179–99.
21. Marino IR, Esquivel CO, Zajco AB *et al*. Distal splenorenal shunt for portal vein thrombosis after liver transplantation. *Am J Gastroenterol* 1989; **1**: 67–70.
22. Rouch DA, Emond JC, Ferrari M, Yousefzadeh D, Whitington P, Broelsch CE. The successful management of portal vein thrombosis after hepatic transplantation with a splenorenal shunt. *Surg Gynecol Obstet* 1988; **166**: 311–16.

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Management of traumatic liver injuries

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Liver injuries in Europe are usually caused by blunt trauma and a high mortality rate is generally reported. The severity of liver injury in 175 patients was graded from I to V and the Injury Severity Score assessed. Seventy-five patients in a prospective study (1987–1990) were treated according to a defined protocol. Non-operative management was used for those who were haemodynamically stable on admission. In unstable patients who proceeded to surgery, liberal use of packing was made and a low threshold for relaparotomy employed. Increasing experience resulted in fewer indications for resection and a 40 per cent rate of non-operative treatment in the prospectively managed group. The overall mortality rate was 12 per cent (15 per cent in the retrospective and 8 per cent in the prospective group). Death in patients with multiple injuries should only rarely result from liver trauma.

The mortality rate from liver trauma has fallen from 60 per cent at the beginning of this century, to 30 per cent during World War II, to current values of 0–10 per cent for penetrating[1,2] and 10–20 per cent for blunt[1–4] injury. Better knowledge of liver pathophysiology and anatomy, and enhanced resuscitation, anaesthesia and intensive care, have contributed to this improvement[5]. Blunt trauma to the abdomen from accidents or sporting misadventures is responsible for 80–90 per cent of all liver injuries in Europe[3,4]. After the spleen, the liver is the most frequently injured organ within the abdominal cavity[4,6]. Most blunt injuries occur in patients with associated and multiple injuries. These usually account for the mortality[1,4,7,8].

Treatment strategies range from an aggressive operative approach[9–12] to a conservative or non-operative expectant policy[13–21]. Diagnostic strategy in the emergency room may include immediate ultrasonography and/or computed tomography (CT). Non-operative or surgical treatment is based on preoperative grading of the severity of the liver injury. Based on retrospective experience a management policy has been developed in which the choice of therapy is specifically tailored to the grade of liver injury and condition of the patient on admission[4]. The value and place of non-operative treatment in patients who were stable on admission was assessed.

Patients and methods

A total of 175 patients with liver trauma were examined, 100 retrospectively (1973–1986) and 75 prospectively (1987–1990). The severity of liver injury was graded from I to V, modified after Moore *et al.*[22,23] (*Table 1*). This classification corresponds to the anatomical and pathological pattern of liver trauma and reflects necessary therapeutic measures[4,22] (*Table 2*). Multiple trauma was assessed by the Injury Severity Score (ISS)[24–26] because of the proven value of this score in retrospective and prospective analysis and its known correlation with outcome[25,26].

The prospective group was managed using a defined treatment policy, including early efficient resuscitation (blood and fresh frozen plasma)[27], rapid assessment of associated injuries and determination of priorities of treatment. Immediate ultrasonography[28] and/or CT[29–31] in all stable patients or in those with a head injury was employed for the assessment and diagnosis of hepatic injury. Liver injury grade was determined in all patients treated without operation by CT, acknowledging the inexactitude of the method[29]. Special attention was paid to areas of devascularized liver tissue.

A stable patient was defined as one having a shock index (pulse rate/systolic blood pressure) <1 on admission and a requirement for <2 litres electrolyte solution and <2 units packed red cells over the next 2 h. Management consisted of close supervision on the intensive care unit with repeated ultrasonography, CT or angiography.

Peritoneal lavage was used only in the prospective group in a few unstable patients when ultrasonography was not immediately available.

Table 1 *Classification of liver injury (modified after Moore* et al.[22,23]*)*

Grade	Description of injuries
I	Capsular tear or avulsion Superficial parenchymal injury (<1 cm)
II	Superficial parenchymal injury (1–3 cm deep) Subcapsular haematoma ⩽10 cm Peripheral penetrating wound
III	Deep parenchymal injury (>3 cm) Subcapsular haematoma >10 cm Central penetrating wound Intrahepatic haematoma <3 cm Hilar injury (portal vein branch, hepatic artery branch, hilar ducts)
IV	Massive injury to one lobe Devitalization of more than one segment Intrahepatic haematoma >3 cm Injury to portal vein, hepatic artery or major branch
V	Extensive liver injury to both lobes Bleeding from hepatic veins or vena cava Retrohepatic vena cava injury

Table 2 *Operative treatment and grade of liver injury*

Grade of injury	Treatment
I	Conservative (operative or non-operative), infrared coagulation, suture
II	As for I plus haemostasis: suture, buffers, Teflon (Du Pont, Wilmington, Delaware, USA)
III	As for II plus debridement, resection, tamponade (Pringle manoeuvre may be necessary)
IV	As for III plus resection possible, tamponade, vascular isolation
V	As for IV plus intraoperative vascular isolation

Perihepatic packing may be used in all grades in case of incomplete haemostasis

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Surgery was performed in unstable patients or for suspicion of ongoing haemorrhage or liver necrosis[5,13–16,27,32]. The estimated liver injury grade was confirmed (*Table 1*) and a specific therapeutic manoeuvre chosen accordingly (*Table 2*). All necrotic liver tissue was removed[4,5,9–12,15]. Deep parenchymal injuries were suture ligated if bleeding was present at laparotomy[4,5,15,33]. Resection was carried out in those with severe segmental or lobar injuries and large areas of devascularized and/or infected liver tissue[12–16,27,32]. Packing was used when incomplete haemostasis necessitated a planned 'second-look' operation; a low threshold for relaparotomy for suspected necrosis or recurrent or continued haemorrhage was employed[4,13–16,19–21].

Results

There were 25 female and 75 male patients in the retrospective group with a mean age of 32·6 (range 7–77) years. Blunt trauma occurred in 90 patients and a penetrating injury in ten (six gunshot and four stab wounds). The prospective group comprised 17 female and 58 male patients (mean age 31·2 (range 16–79) years) with 68 blunt and seven penetrating injuries. Liver injury grades are shown in *Figure 1*.

The mean ISS of the patients was 33. The CT-estimated liver injury in patients treated without operation was grade I or II in 17 patients and grade III or IV in 13. The overall mortality rate was 12 per cent: 15 per cent in the retrospective and 8 per cent in the prospective group. The overall mortality rate in the 158 patients with blunt trauma was 13 per cent; in the 17 with a penetrating injury there were no deaths. In the retrospective group, death occurred in six patients with grade I or II liver injuries, in four with grade III injury, in four with grade IV trauma and in the one patient with a grade V injury. No patient died from immediate exsanguination but four succumbed to continued haemorrhage from the liver. Five patients died with complications of concomitant multiple injuries (acute respiratory distress syndrome (ARDS), multiple organ failure, pneumonia, sepsis). Six patients died from head injuries.

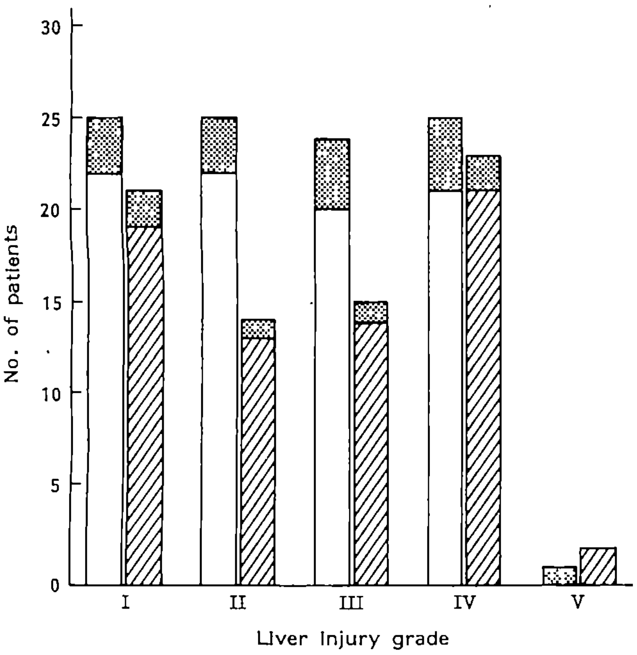

Figure 1 *Liver injury grade* versus *mortality in retrospective* (□) *and prospective* (■) *groups.* ▨, *Patients who died*

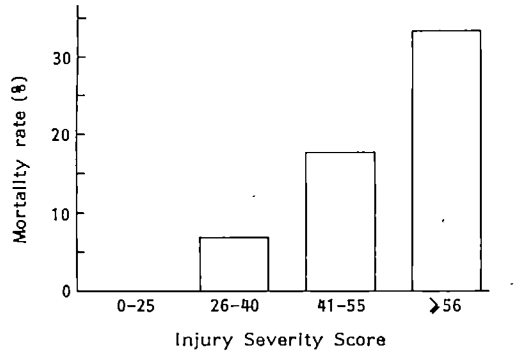

Figure 2 *Injury Severity Score* versus *mortality rate*

Table 3 *Incidence of hepatic resection and mortality in patients undergoing resection (liver injury grades IV and V)*

	Retrospective group (n = 100)	Prospective group (n = 75)	Total (n=175)
Patients undergoing resection	20 (20)	10 (13)	30 (17)
Mortality following resection	6 (30)	0 (0)	6 (20)

Values in parentheses are percentages

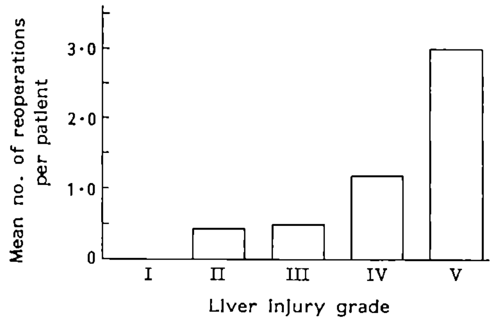

Figure 3 *Mean number of reoperations* versus *liver injury grade*

In the prospective group one patient with haemophilia died after being referred 14 h after a first operation as a direct consequence of the coagulation disorder. Two patients died late from pulmonary embolism in spite of low-dose heparin prophylaxis. The fourth patient, following an attempted suicide by drowning, died from ARDS. One patient (liver injury grade II, ISS 50) died from massive haemorrhage caused by multiple injuries. One patient with a liver injury treated without operation (grade IV) died on the 16th day after admission from multiple organ failure (ISS 59). In the prospective group the two patients with grade V liver trauma (retrohepatic vena cava injury) survived following the use of intraoperative vascular exclusion[5,20]. The approach to the suprahepatic vena cava was intrapericardial after median sternotomy in one and infra-diaphragmatic from the left side, as in liver transplantation, in the other. This method proved reliable and safe.

For all patients the ISS accurately predicted survival (*Figure 2*). No patient with liver injury alone died. The mortality rate increased with the number of concomitant injuries (*Figure 2*). Twenty-one of 71 patients admitted directly to the unit had a shock index ⩾1; the mortality rate in these was 14 per cent compared with 2 per cent in those with a shock index <1 on admission.

Thirty patients required hepatic resection, giving an overall resection rate of 17 per cent (*Table 3*). Only three patients were treated without operation in the retrospective group compared with 30 in the prospective group. Two of the patients treated without operation with a CT-estimated liver injury of grade IV developed vascular complications (false aneurysm and an arterial–portal venous fistula) which necessitated radiological embolization. Reoperations increased with the grade of liver injury (*Figure 3*). The overall treatment methods are shown in *Table 4*.

Table 4 *Treatment methods*

	Retrospective group ($n = 100$)	Prospective group ($n = 75$)	Total ($n = 175$)
Conservative	3 (3)	30 (40)	33 (19)
Operative	97 (97)	45 (60)	142 (81)
Minor	90	42	132
Arterial ligation	6 (6)	0 (0)	6 (3)
Tamponade	11 (11)	12 (16)	23 (13)
Resection	20 (20)	10 (13)	30 (17)
Reoperations	46	36	82

Values in parentheses are percentages

Discussion

The main difference between the retrospective and prospective groups was that in the former there was no defined protocol. In the prospective group, treatment was conducted according to a policy based on early assessment of the liver and multiple injury grade, and haemodynamic stability. This allows a more deliberate selection of cases for non-operative management[4,5,13–18,20,21,28–31], particularly in younger patients with subcapsular or intrahepatic rupture. Delayed rupture and vascular complications must be considered[30,31]. Because of the potential vascular complications in grade IV liver injuries treated without operation, routine angiography is recommended. All patients treated without operation with a CT-estimated liver injury of grade III or IV should undergo angiography 10 days and 3 months after trauma.

In unstable patients, surgical intervention under optimal conditions is mandatory. Emergency room laparotomy is contraindicated[34]. Extensive debridement of all necrotic liver tissue is necessary and hepatic resection may be required[4,19,32]. Arterial ligation is contraindicated[35]. Provisional haemostasis (especially tamponade) with planned early reoperation was frequent in the prospective series and was, as elsewhere, of great value[4,5,13–16,20,21] (*Table 4; Figure 3*). In retrohepatic injuries an element of self-tamponade takes place that may be disturbed by misguided early exploration.

Mortality was due mostly to concomitant injuries (*Figure 2*) and rarely to liver trauma. There are few studies that differentiate and grade both the severity of liver trauma and the extent of associated injuries[1,4,7]. Improvement of the results of treatment of liver injury can be achieved only by improving the whole chain of treatment. The main points are: immediate stabilization of vital functions with early transfusion of erythrocyte concentrates and fresh frozen plasma; non-operative treatment in patients stable on admission (ultrasonography, CT, angiography, intensive care); familiarity of the surgeon with the surgical, anatomical and pathophysiological principles of hepatic surgery; a conservative operative approach to liver injury with tamponade whenever definite haemostasis and/or resection seems dangerous; resection restricted to removal of necrotic and/or infected liver tissue; and a low threshold for early relaparotomy.

References

1. Little JM, Fernandez A, Tait M. Liver trauma. *Aust N Z J Surg* 1986; **56**: 613–19.
2. Carmona RH, Lim RC, Clark GC. Morbidity and mortality in hepatic trauma. *Am J Surg* 1982; **144**: 188–94.
3. Mätsch T, Bergquist D, Hedelin M, Findbläck B. Leberverletzungen nach stumpfem Bauchtrauma. *Unfallchirurgie* 1982; **85**: 524–8.
4. Schweizer W, Tanner S, Baer HU, Huber A, Berchtold R, Blumgart LH. Diagnostik und Therapie von Leberverletzungen beim polytraumatisierten Patienten. *Helv Chir Acta* 1989; **55**: 597–612.
5. Donovan AJ, Berne TV, Dawson J, Stone HH, Sandblom Ph. Liver injury. In: Blumgart LH, ed. *Surgery of the Liver and Biliary Tract*. Edinburgh: Churchill Livingstone, 1988: 1033–89.
6. Moore EE, Eisemann B, Dunn EL. Current management of hepatic trauma. *Contemporary Surgery* 1979; **15**: 91–115.
7. Aldrete JS. Current management of traumatic injuries to the liver. *Ala Med* 1985; **55**: 44–8.
8. Walt AJ. The mythology of hepatic trauma – or Babel revisited. *Am J Surg* 1978; **135**: 12–18.
9. Blumgart LH, Vajrabukka J. Injuries to the liver: analysis of 20 cases. *BMJ* 1972; **i**: 158–64.
10. Donovan AJ, Michaelian MJ, Yellin AE. Anatomical hepatic lobectomy in trauma to the liver. *Surgery* 1973; **73**: 833–47.
11. Balasegaram M, Joishy SK. Hepatic resection: the logical approach to surgical management of major trauma to the liver. *Am J Surg* 1981; **142**: 580–3.
12. Hollands MJ, Little JM. The role of hepatic resection in the management of blunt liver trauma. *World J Surg* 1990; **14**: 478–82.
13. Calne RY, McMaster P, Pentlow BD. The treatment of major liver trauma by primary packing with transfer of the patient for definitive treatment. *Br J Surg* 1979; **66**: 338–9.
14. Calne RY, Wells FC, Forty J. Twenty-six cases of liver trauma. *Br J Surg* 1982; **69**: 365–8.
15. Watson CJE, Calne RY, Padhani AR, Dixon AK. Surgical restraint in the management of liver trauma. *Br J Surg* 1991; **78**: 1071–5.
16. Editorial. Managing liver trauma conservatively. *Lancet* 1991; **338**: 1429–30.
17. Athey GN, Rahman SU. Hepatic hematoma following blunt injury: non-operative management. *Injury* 1982; **13**: 302–6.
18. Andersson R, Bengmark S. Conservative treatment of liver trauma. *World J Surg* 1990; **14**: 483–6.
19. Stirnemann H. Die zweizeitige Versorgung von unübersichtlichen schweren Leberrupturen. *Chirurg* 1984; **45**: 550–3.
20. Cue JI, Cryer HG, Miller FB, Richardson JD, Polk HC. Packing and planned reexploration for hepatic and retroperitoneal hemorrhage: critical refinements of a useful technique. *Trauma* 1990; **30**: 1007–13.
21. Carmona RH, Deck DZ, Lim RC. The role of packing and planned re-operation in severe hepatic trauma. *J Trauma* 1984; **24**: 779–84.
22. Moore EE. Critical decisions in the management of hepatic trauma. *Am J Surg* 1984; **148**: 712–16.
23. Moore EE, Shackford SR, Pachter HL *et al.* Organ injury scaling: spleen, liver and kidney. *Trauma* 1989; **29**: 1664–6.
24. Baker SP, O'Neil B, Haddon W, Long WB. The Injury Severity Score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma* 1974; **14**: 187–96.
25. Schneck HJ, Tempel G, von Hundelshausen B, Brosch R. Der Injury Severity Score (ISS) zur Klassifizierung polytraumatisierter Patienten. *Zentralbl Chir* 1986; **111**: 1025–33.
26. Schneck HJ, von Hundelshausen B, Tempel G, Brosch R. Die Aussagekraft des Injury Severity Score (ISS). *Aktuel Traumatol* 1985; **15**: 249–53.
27. Lim RC, Lau G, Steele M. Prevention of complications after liver trauma. *Am J Surg* 1976; **132**: 156–61.
28. Lam AH, Shulman L. Ultrasonography in the management of liver trauma in children. *J Ultrasound Med* 1984; **3**: 199–203.
29. Croce MA, Fabian TC, Kudsk KA *et al.* AAST Organ Injury Scale: correlation of CT-graded liver injuries and operative findings. *J Trauma* 1991; **31**: 806–12.
30. Meyer AA, Crass RA, Lim RC, Jeffrey RB, Federle MP, Trunkey DD. Selective nonoperative management of blunt liver injury using computed tomography. *Arch Surg* 1985; **120**: 550–4.
31. Moon KL, Federle MP. Computed tomography in hepatic trauma. *AJR Am J Roentgenol* 1983; **141**: 309–14.
32. Smadja C, Traynor O, Blumgart LH. Delayed hepatic resection for major liver injury. *Br J Surg* 1982; **69**: 361–4.
33. Wood CB, Chapperauld I, Blumgart LH. Bioplast fibrin buttons for liver biopsy and partial liver resection. *Ann R Coll Surg Engl* 1976; **58**: 401–4.
34. Eisner L, Ackermann C, Regazzoni P, Harder F. Therapie und Prognose bei 102 Leberverletzungen. *Helv Chir Acta* 1988; **55**: 593–6.
35. Flint CM, Polk HC. Selective hepatic arterial ligation: limitations and failures. *J Trauma* 1979; **19**: 319–23.

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Traumatic pancreatic pseudocysts

Fifteen patients who developed pseudocysts following pancreatic trauma were evaluated to determine outcome in relation to the nature and site of pancreatic duct injury. Pseudocysts developed in eight patients operated on within 48 h of abdominal trauma and in seven who were initially treated conservatively. In none was duct injury diagnosed during initial management. Presentation was a median of 20 (range 8–360) days after injury. In 14 patients, pseudocysts (mean diameter 9 (range 3–16) cm) were confirmed by computed tomography or ultrasonography. Endoscopic retrograde pancreatography (ERP) demonstrated the site and severity of the duct injury in eight of 11 patients. Two patients with side duct injury on ERP were treated successfully without intervention. Pseudocysts arising from distal duct injuries (four patients) were treated by percutaneous aspiration or catheter drainage, although one patient required subsequent distal resection for recurrent pancreatitis caused by a pancreatic duct stricture. Three patients with duct injuries in the neck or body with pancreatic disruption underwent distal pancreatectomy. Proximal duct injuries with mature pseudocysts (three patients) were drained internally. Three patients had complicated pseudocysts (haemorrhage in one, sepsis in two) that necessitated emergency laparotomy and external drainage; one of these patients died from sepsis. These findings suggest that traumatic pancreatic pseudocysts that follow peripheral duct injury may resolve spontaneously, whereas those associated with distal duct injuries can be treated by percutaneous aspiration or catheter drainage. Proximal duct injuries, however, require surgical intervention using either resection or internal drainage, depending on the maturity of the cyst wall.

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Trauma to the pancreas is uncommon and constitutes only 1–2 per cent of all abdominal injuries[1]. Associated major vascular and visceral injuries are common and are mainly responsible for the mortality rate of up to 40 per cent[2]. Blunt trauma to the pancreas may be clinically occult and duct injury may go unrecognized during initial evaluation or at the time of surgery. Delay in diagnosis is associated with increased morbidity and hospitalization. Major early complications including abscess, haemorrhage, pancreatic fistula or pseudocysts are reported to develop in one-third of surviving patients[3].

Because of the comparative rarity of the late sequelae of pancreatic injury, clinical experience of the optimal therapy for post-traumatic pancreatic pseudocysts is limited. The present study reports a series of 15 patients who developed pancreatic pseudocysts after trauma and evaluates the outcome in relation to the nature and site of the pancreatic duct injury.

Patients and methods

The records of 64 consecutive patients who had sustained proven pancreatic trauma between January 1980 and December 1989 were reviewed. Fifteen patients (13 men, two women) of mean age 35 (range 24–68) years developed a post-traumatic pancreatic pseudocyst. Eleven patients suffered blunt trauma (ten assault, one motor vehicle accident) and four had penetrating injuries (three gunshot, one knife wound).

The outcome of treatment was reviewed with regard to other organ injury, initial management, complications and the site and extent of pancreatic duct injury. Ultrasonography and computed tomography (CT) were used to determine the location and size of the pseudocyst and, whenever possible, the site and nature of the pancreatic duct injury was assessed by endoscopic retrograde pancreatography (ERP).

Results

Initial management

Eight of the 15 patients underwent abdominal exploration within 48 h of injury. Five of these eight patients had a laparotomy within 4 h of the initial trauma and three were initially managed conservatively but subsequently required laparotomy for deteriorating abdominal signs. Four patients had isolated pancreatic injuries and four required other procedures including management of liver lacerations (three patients), splenectomy (one) and nephrectomy (one). One patient underwent repair of the inferior vena cava, gallbladder, duodenum, small bowel and stomach. Pancreatic injury (retroperitoneal haematoma (four patients), capsular tear (two) or peripheral disruption of pancreatic parenchyma (one)) was noted in seven patients but missed in one with a major liver injury. In none was pancreatic duct involvement recognized. Management of the pancreatic injury was limited to drainage in six patients; in two patients no drains were used. A pancreatic pseudocyst subsequently developed in all eight of these patients after the initial surgical management. In seven patients, duct injury was later demonstrated in the pancreatic head (one patient), neck (one), body (three) and tail (two).

The remaining seven patients were initially managed without operation as they had minimal abdominal signs on presentation after blunt abdominal trauma. In one patient (no. 2 in *Table 1*) with minimal abdominal signs but a raised serum amylase level, ERP 24 h after injury showed minor duct disruption in the uncinate process (*Figure 1*) and limited extravasation of contrast. A pseudocyst subsequently developed in this patient. The remaining six patients presented 9, 16, 18, 20, 240 and 360 days after the initial injury with a symptomatic pancreatic pseudocyst.

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Table 1 *Outcome after non-operative management of traumatic pancreatic pseudocysts*

			Duct injury		Pseudocyst				
Patient no.	Age (years)	Sex	Type	Site	Delay in presentation (days)	Size (cm)*	Management	Duration of hospital stay (days)	Outcome
2	30	M	Blunt	Head	12	10	Conservative	18	Well
10	33	F	Stab	Body	24	7	Conservative	37	Well
11	32	M	Blunt	Body	9	14	Percutaneous aspiration (3 times) Percutaneous drainage for 21 days plus octreotide	50	Fistula, stricture, distal pancreatectomy
13	25	M	Gunshot	Tail	16	5	Percutaneous drainage for 32 days plus octreotide	36	Fistula
14	45	F	Blunt	Tail	30	13	Percutaneous aspiration (3 times)	40	Well
15	33	M	Blunt	Tail	32	16	Percutaneous aspiration (once)	16	Well

*Determined by ultrasonography or computed tomography

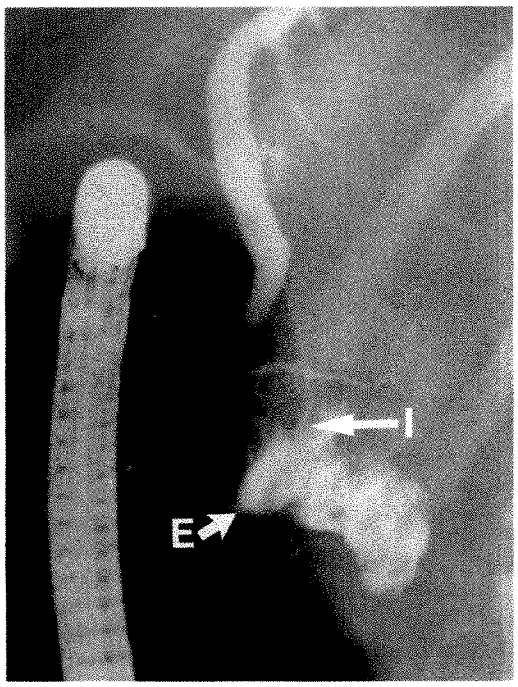

Figure 1 *Endoscopic retrograde pancreatography in patient 2. There is extravasation (E) of contrast after peripheral duct injury (I) in the uncinate process*

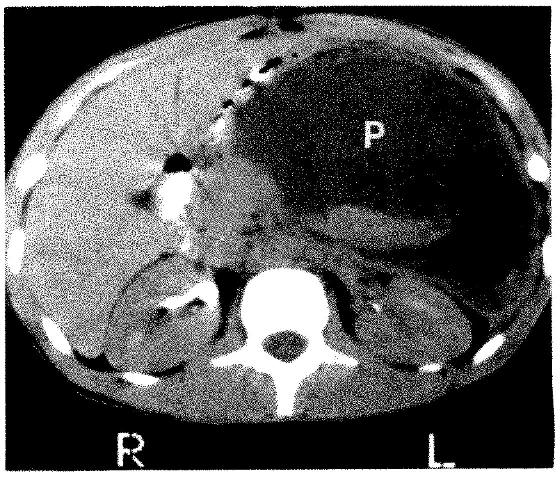

Figure 2 *Computed tomography demonstrating a large pseudocyst (P) following blunt pancreatic trauma*

Investigation of pseudocyst

The mean diameter of the pseudocysts was 9 (range 3–16) cm (*Figure 2*). Pseudocysts were demonstrated in 14 of the 15 patients by either ultrasonography (11 patients) and/or CT (nine cases) (*Tables 1* and *2*). Patient 12, in whom neither investigation was performed before operation, had an acute major bleed into the pseudocyst, which required urgent surgical intervention and external drainage while awaiting investigation.

ERP was successful in eight of 11 patients (*Figure 3*). In three, submucosal and intramural duodenal haematoma obscured the papilla and prevented intubation of the pancreatic duct. One further patient had intraoperative pancreatography performed through the ampulla of Vater. Evidence of duct injury was present in all nine patients. In a further four, pancreatic duct injury was noted during operation at the time of surgical management of the pseudocyst. *Figure 4* shows the sites of duct injury in 13 patients. In two patients (nos 12 and 15), main pancreatic duct injury was not demonstrated.

Treatment

Two patients (nos 2 and 10) were stable with mild abdominal symptoms and had contained extravasation of contrast from a small peripheral pancreatic duct injury on ERP. Both were treated conservatively and showed complete resolution of the pseudocyst on ultrasonography at 3 and 6 months.

Four patients with a pancreatic pseudocyst (nos 11, 13, 14 and 15) underwent either percutaneous needle aspiration or catheter drainage (*Table 1*). The cyst was emptied as completely as possible by aspiration using a 22-G Chiba needle positioned with ultrasonographic guidance. Fluid samples were submitted for bacterial culture and amylase estimation. In all, seven aspirations were performed in three patients. All collections were sterile on culture and the amylase level in all was $>45\,000$ units/l. Two patients showed complete resolution after one and three aspirations. The pseudocyst in the third patient (no. 11) recurred after three aspirations and required percutaneous catheter drainage for 21 days with parenteral alimentation and octreotide (Sandostatin; Sandoz, Randburg, South Africa) therapy before complete resolution. This patient had a duct injury in the mid-body of the pancreas and developed recurrent pancreatitis secondary to a pancreatic duct stricture, which required distal pancreatectomy 11 months after the initial injury. The fourth patient with a duct injury in the pancreatic tail (no. 13) was treated by percutaneous catheter drainage plus octreotide. The drainage resolved after 32 days.

Nine patients were managed by operation (*Table 2*). The

Table 2 *Outcome after operative management of traumatic pancreatic pseudocysts*

Patient no.	Age (years)	Sex	Duct injury		Pseudocyst		Surgery	Hospital stay after diagnosis of pseudocyst (days)	Outcome
			Type	Site	Delay in presentation (days)	Size (cm)*			
1	27	M	Gunshot	Head	24	7	External drainage	15	Fistula, died
3	68	M	Blunt	Neck	360	3	Roux-en-Y cystojejunostomy	14	Well
4	41	M	Blunt	Neck	20	6	Distal pancreatectomy	32	Fistula
5	26	M	Gunshot	Body	240	10	Roux-en-Y cystojejunostomy	21	Well
6	37	M	Blunt	Body	13	7	Distal pancreatectomy	20	Well
7	24	M	Blunt	Body	8	6	External drainage	37	Fistula
8	37	M	Blunt	Body	18	11	Roux-en-Y cystojejunostomy	90	Fistula
9	24	M	Blunt	Body	70	9	Distal pancreatectomy	80	Fistula, abscess
12	38	M	Blunt	Body	14	12†	External drainge	26	Well

*Determined by ultrasonography or computed tomography; †measured at laparotomy

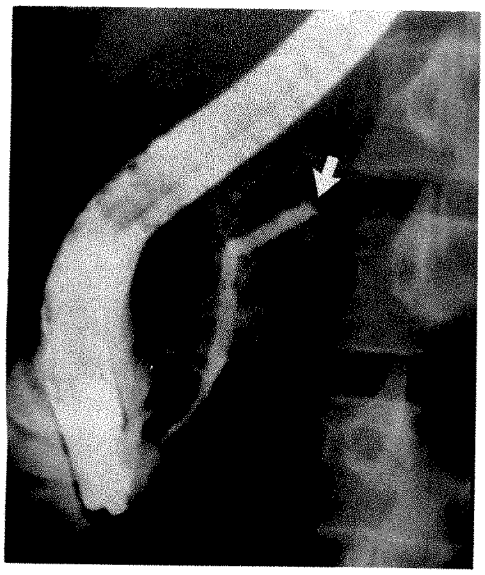

Figure 3 *Endoscopic retrograde pancreatography showing complete main duct occlusion, indicating duct injury (arrow) in the pancreatic neck*

three patients (nos 4, 6 and 9) who had complete disruption of the pancreas in the neck or body were treated by distal pancreatectomy. Internal drainage of the pseudocyst by a Roux-en-Y cystojejunostomy was performed in three patients (nos 3, 5 and 8) with mature cysts related to duct injuries in the pancreatic neck or body. Three patients (nos 1, 7 and 12) required emergency surgery for pseudocysts complicated by sepsis (two patients) or bleeding (one); these were managed by control of the haemorrhage in one and external tube drainage in all.

Outcome

One patient died 39 days after trauma from multiorgan failure related to sepsis after a bullet injury to the pancreatic head. The median duration of hospitalization in the 14 survivors was 34 (range 14–90) days. Pancreatic fistulas occurred in seven patients following distal resection (two patients), Roux-en-Y cystojejunostomy (one), operative tube drainage (two) and percutaneous drainage (two). The one death (patient 1; *Figure 4*) was a result of a high-output fistula complicated by sepsis and multiorgan failure. The fistulas in the remaining six patients persisted for a mean of 23 (range 8–40) days. Two of these fistulas ceased to drain after treatment with octreotide for 7 and 14 days respectively. Four of the five patients who were managed by either percutaneous drainage (two patients) or operative external drainage (three) developed fistulas. All four of these patients had demonstrable duct injury on ERP (two patients) or operative findings (two). No patient developed either pancreatic insufficiency or diabetes on subsequent follow-up.

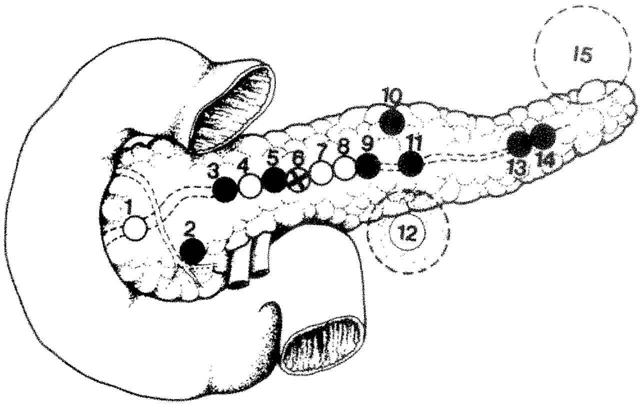

Figure 4 *Site of pancreatic duct injury in patients 1–15 demonstrated by:* ●, *endoscopic retrograde pancreatography;* ○, *operative findings; and* ⊗, *operative pancreatography. In two cases no duct injury was detected:* ⑫, *pseudocyst confirmed at emergency laparotomy;* ⑮, *pseudocyst shown on computed tomography*

Discussion

The results of the present study reflect the diagnostic difficulty encountered both in determining pancreatic injury clinically after blunt abdominal trauma and in assessing the presence of pancreatic duct injury at laparotomy. In seven of the 15 patients who developed pancreatic pseudocysts, abdominal injury was thought initially to be minor and not to warrant laparotomy; in eight patients duct injury was missed at operation. In addition, it was found that the clinical manifestations of isolated pancreatic injury and undetected duct disruption may be delayed for substantial periods and become apparent only when complications develop. Previous reports[4–6] have noted that undetected duct disruption may result in continued leakage of pancreatic enzymes, causing pancreatic pseudocyst, fistula, ascites or recurrent pancreatitis. In the present series, pseudocysts presented 8–360 (mean 59) days after the initial trauma. Other authors have also noted a delayed presentation of complications, ranging from 6 months to 21 years after the original pancreatic injury[5,6].

Although the combination of ultrasonography and CT in the present study was accurate in demonstrating pseudocyst formation when it occurred as a delayed complication of pancreatic injury, the role of these investigations in determining acute pancreatic injury is less well established[7]. Whereas CT has been reported to identify 97 per cent of solid visceral injuries accurately[8], acute pancreatic injuries may be missed by CT in 20 per cent of cases because of poor visualization in the presence of multiple trauma[9]. CT has been critically evaluated in two studies of patients with acute pancreatic injury[7,10]. In an analysis of 300 patients undergoing CT after abdominal trauma, Jeffrey *et al.*[10] correctly identified 13 pancreatic injuries but noted two false-positive and two false-negative reports. Cook *et al.*[11] identified five pancreatic injuries in 82 patients but incorrectly identified seven as having pancreatic injuries. Although CT may be a useful screening method for excluding pancreatic injury, it is unable to identify duct injury accurately unless there is complete transection of the gland. A combination of CT with ERP has allowed early detection of major duct injuries[12].

Successful surgical management of pancreatic trauma depends on precise delineation of the extent of injury. Detection of duct injury may be difficult and gross inspection and palpation can be misleading. Retroperitoneal or subcapsular haematoma and oedema may mask major parenchymal disruption and may limit adequate pancreatic evaluation. In the eight patients in this study explored within 48 h of trauma, no ductal injury was suspected. Several authors[3,13] have emphasized the need for adequate duct evaluation and have advocated either intraoperative transduodenal pancreatography or cannulation of the duct in the pancreatic tail. Berni *et al.*[13] reported a threefold reduction in morbidity rate after the introduction of operative pancreatography. Although the addition of a duodenotomy to perform transpapillary pancreatography may potentially increase morbidity from duodenal fistula, this was not found to be a practical problem[13]. Others[14,15] have judged this procedure to be complicated and unnecessary in the acute situation.

The reliability of ERP in identification of duct injury has been reported previously[5,12]. If the patient is clinically stable, several authors[16–19] have recommended pancreatic duct evaluation by preoperative ERP to avoid the potential complications of duodenotomy. Although intraoperative ERP is feasible, its widespread application is limited by logistic and technical factors, particularly in the trauma situation[20,21]. Disruption of the duct can occur in any of the anatomical subdivisions of the pancreas and more than one region may be involved[5]. In addition, strictures or disruption may remain undetected unless imaging is undertaken before definitive surgery[5]. The main benefit of ERP in the present study was in delayed cases which presented with a pseudocyst. ERP enabled accurate identification of the site of duct injury, which influenced the selection of optimal therapy. Precise localization was less accurate with either CT or ultrasonography, since these demonstrated the pseudocyst rather than the site of pancreatic duct injury.

Although the experience of paediatric surgeons indicates that half of traumatic pseudocysts occurring in children will resolve with medical therapy alone[4], only two patients in this adult series had spontaneous resolution of the pseudocyst. Neither of these patients had major duct injury demonstrated on ERP. Percutaneous drainage of pancreatic pseudocysts secondary to alcoholic pancreatitis is now well established as an effective alternative to surgery in selected cases[22]. Few data, however, are available for post-traumatic pseudocyst aspiration in adults. In two of the three patients who underwent initial percutaneous aspiration of the pseudocyst, one and three aspiration sessions were sufficient. The pseudocyst in one patient failed to resolve after aspiration alone and required percutaneous catheter drainage, coupled with intravenous alimentation and octreotide, for 21 days to achieve complete resolution. This patient ultimately required distal pancreatectomy 11 months later for recurrent acute pancreatitis caused by pancreatic duct stricture. One patient treated initially by percutaneous drainage had a persistent fistula and required octreotide before resolution occurred. It was found that percutaneous aspiration or drainage was safe for distal post-traumatic pseudocysts. Since it is the least invasive management, aspiration should be considered as the first-line treatment of post-traumatic pancreatic pseudocysts in the tail that have failed to settle on conservative management. In this group, surgery should be reserved for failure of aspiration of the pseudocyst and for cases in which other complications of the trauma demand exploration. Three patients in this study required urgent intervention for acute complications of the pseudocyst. The major disadvantage of external drainage, either surgical or percutaneous, was the high incidence of pancreatic fistula after intervention. This may persist for prolonged periods and may require parenteral alimentation and octreotide to achieve resolution.

Surgical strategy in the management of traumatic pancreatic pseudocysts will depend on the site and nature of the duct injury, the maturity of the cyst wall and the urgency of the operation. When elective surgical exploration is undertaken for symptomatic cysts, preoperative ERP allows accurate anatomical delineation of the duct injury and facilitates operative strategy. On the basis of this study it is recommended that, if there is minimal communication with a side duct or distal main duct injuries, conservative treatment or aspiration should be attempted. External drainage may lead to prolonged fistula drainage and the role of octreotide in this setting requires further evaluation. Pseudocysts with proximal major duct injury require surgical intervention using either resection or internal drainage, depending on the maturity of the cyst wall.

References

1. Glancy KE. Review of pancreatic trauma. *West J Med* 1989; **151**: 45–51.
2. Northrup WF, Simmons RL. Pancreatic trauma: a review. *Surgery* 1972; **71**: 27–43.
3. Bach RD, Frey CF. Diagnosis and treatment of pancreatic trauma. *Am J Surg* 1971; **121**: 20–9.
4. Burnweit C, Wesson D, Stringer D, Filler R. Percutaneous drainage of traumatic pancreatic pseudocysts in children. *Trauma* 1990; **30**: 1273–7.
5. Carr ND, Cairns SJ, Lees WR, Russell RCG. Late complications of pancreatic trauma. *Br J Surg* 1989; **76**: 1244–6.
6. Leppaniemi A, Haapiainen R, Kiviluoto T, Lempinen M. Pancreatic trauma: acute and late manifestations. *Br J Surg* 1988; **75**: 165–7.
7. Dodds WJ, Taylor AJ, Erickson SJ, Lawson TL. Traumatic fracture of the pancreas: CT characteristics. *J Comput Assist Tomogr* 1990; **14**: 375–8.
8. Balthazar EJ, Chako AC. Computerized tomography in acute gastrointestinal disorders. *Am J Gastroenterol* 1990; **85**: 1445–52.
9. Jurkovich GJ, Carrico CJ. Pancreatic trauma. *Surg Clin North Am* 1990; **70**: 575–93.
10. Jeffrey RB, Federle MP, Crass RA. Computer tomography of pancreatic trauma. *Radiology* 1983; **147**: 491–4.
11. Cook DG, Walsh JW, Vick CW, Brewer WH. Upper abdominal trauma: pitfalls in CT diagnosis. *Radiology* 1986; **159**: 65–9.
12. Whitwell AE, Gomez GA, Byers P, Kreis DJ, Manten H, Casillas VJ. Blunt pancreatic trauma: prospective evaluation of early endoscope retrograde pancreatography. *South Med J* 1986; **82**: 586–91.
13. Berni GA, Bandyk DF, Oreskovich MR, Carrico CJ. Role of intraoperative pancreatography in patients with injury to the pancreas. *Am J Surg* 1982; **143**: 602–5.
14. Feliciano DV, Martin TD, Cruse PA *et al.* Management of combined pancreatoduodenal injuries. *Ann Surg* 1987; **205**: 673–9.
15. Jones RC. Management of pancreatic trauma. *Am J Surg* 1985; **150**: 698–704.
16. Laraja RD, Lobbato VJ, Cassaro S, Reddy SS. Intraoperative endoscopic retrograde cholangiopancreatography in penetrating trauma of the pancreas. *J Trauma* 1986; **26**: 1146–7.
17. Taxier M, Sivak MV, Cooperman AM, Sullivan BH. Endoscopic retrograde pancreatography in the evaluation of trauma to the pancreas. *Surg Gynecol Obstet* 1980; **150**: 65–8.

18. Hayward SR, Lucas CE, Sugawa C, Ledgerwood AM. Emergent endoscopic retrograde cholangiopancreatography. *Arch Surg* 1989; **124**: 745–6.
19. Hall RI, Lavelle MI, Venables CW. Use of ERCP to identify the site of traumatic injuries of the main pancreatic duct in children. *Br J Surg* 1986; **73**: 411–12.
20. Sugawa C, Lucas CE. The case for preoperative and intraoperative ERCP in pancreatic trauma. *Gastrointest Endosc* 1988; **34**: 145–7.
21. Barkin JS, Ferstenberg RM, Panullo W, Manten HD, Davis RC. Endoscopic retrograde cholangiopancreatography in pancreatic trauma. *Gastrointest Endosc* 1988; **34**: 102–5.
22. Colhoun E, Murphy JJ, MacErlean DP. Percutaneous drainage of pancreatic pseudocysts. *Br J Surg* 1984; **71**: 131–2.

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Case report

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Symptomatic wandering spleen

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Wandering spleen is a rare condition[1] in which the organ is attached by an abnormally long vascular pedicle without the usual peritoneal ligaments. Torsion of the spleen is a life-threatening consequence presenting as either an emergency or chronic condition. This is the first report of a symptomatic case in which there was no evidence that torsion had occurred; it was treated successfully by splenopexy.

Case report

A 31-year-old Asian woman, parity two, presented with a 3-year history of left-sided abdominal pain. In addition a tender firm lump was present in the left upper quadrant when the patient lay on the right side. On repeated examination, mild tenderness could be elicited in the left hypochondrium and there was evidence of a tender swelling below the left ribs, particularly when the patient was rolled to the right. This swelling was palpable only momentarily and seemed to slip away from the examining fingertips and disappear as soon as contact was made. There was no cough impulse. These symptoms and signs remained unchanged for 12 months; during this time the patient underwent blood tests, abdominal ultrasonography, barium enema and intravenous urography, results from all of which were normal. After full discussion with the patient it was decided to perform exploratory laparotomy.

Examination under anaesthesia was normal and at operation there was no sign of abdominal wall herniation. The spleen was found to be unusually mobile and prolapsed easily into the upper midline wound. Its appearance and dimensions were within normal limits, with no sign of chronic venous congestion. It was felt that the apparent swelling was caused by anterior and inferior excursion of the organ. Splenopexy was therefore performed, attaching the stomach to the diaphragm and lateral abdominal wall with polyglactin 910 sutures, thus fixing the spleen in the normal anatomical position. The patient made an uneventful recovery and at follow-up symptoms and signs had resolved completely.

Discussion

Many theories have been suggested for the aetiology of wandering spleen. Multiparity can increase abdominal laxity[2], splenomegaly may elongate the vascular pedicle by constant traction[2], or the usual peritoneal ligaments may be congenitally malformed[3]. Longstanding symptoms are usually associated with chronic or recurrent torsion, which causes chronic venous congestion and thus splenomegaly and perisplenic adhesions. The blood profile becomes distorted, with leucopenia and thrombocytopenia[4]. None of these features was evident in this case. Although splenectomy has been the usual treatment for torsion of the spleen, conservation is now advisable. This report illustrates that symptoms may be present without torsion and may be resolved in such cases by splenopexy.

References

1. Pugh HL. Splenectomy, with special reference to historical background: indications and rationale, and comparison of reported mortality. *International Abstracts of Surgery* 1946; **84**: 209–24.
2. Abell I. Wandering spleen with torsion of the pedicle. *Ann Surg* 1933; **98**: 722–35.
3. Woodward DAK. Torsion of the spleen. *Am J Surg* 1967; **114**: 953–5.
4. Weinreb NJ, Bauer J, Dikman S *et al.* Torsion of the spleen as a rare cause of hypersplenism. *JAMA* 1974; **230**: 1015–16.

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Assessment of main pancreatic duct integrity by endoscopic retrograde pancreatography in patients with acute pancreatitis

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The integrity of the main pancreatic duct (MPD) was evaluated by endoscopic retrograde pancreatography (ERP) in a retrospective study of 105 patients with acute pancreatitis presenting over an 11-year period (1980–1991). The findings were compared with clinical outcome and the need to operate for local pancreatic complications. Patients were divided into two groups. Group 1 (n = 89) had either clinically mild pancreatitis or severe disease but no surgery for local complications, and <25 per cent necrosis on contrast-enhanced computed tomography (CT) (n = 48). Group 2 patients (n = 16) had clinically severe pancreatitis and underwent surgery for local complications and/or had ⩾25 per cent necrosis on CT (n = 12), at surgery or post mortem. All 89 patients in group 1 had an intact MPD at ERP, which was performed a median of 6 (range 0–30) days after onset of pancreatitis; the median age was 63 (range 20–88) years and there were no deaths. The median age of patients in group 2 was 59 (range 26–85) years. ERP in this group was performed in four patients <5 days after onset and all had an intact MPD; one died with necrosis and another from a cerebrovascular accident. ERP was performed ⩾5 days after onset in the other 12 patients: five had an intact MPD and two required surgery for pseudocyst drainage only; seven had a disrupted MPD and all required surgery for pancreatic necrosis (one death). It is concluded that an intact MPD was a feature of mild pancreatitis, whereas disruption occurred >4 days after onset in patients with necrosis necessitating surgery.

The incidence of pancreatic necrosis in unselected cases of acute pancreatitis is 4–5 per cent[1,2] but this is associated with a mortality rate of 20–50 per cent[1,3]. Surgical intervention has been shown to be important in achieving optimal results; the current options include necrosectomy and drainage[1,4], 'open' methods of pancreatic debridement[5,6] and necrosectomy with closed lavage[7,8]. Percutaneous methods of intervention have been described but their place in routine management remains under evaluation[9,10].

Three other aspects of management are critical in determining the outcome of these patients. First is the early institution of intensive medical treatment, in particular circulatory and pulmonary support[11]. Second is the identification and determination of the extent of pancreatic necrosis; this can now be effectively achieved by rapid large-bolus contrast-enhanced computed tomography (CT)[5–10,12]. Third is the timing of intervention, which is based on less precise criteria involving clinical judgement in conjunction with a variety of indicators. The latter include the APACHE II score[13] and biochemical markers such as C-reactive protein[14] and phospholipase A_2[15].

In 1983, Gebhardt *et al.* from Erlangen in Germany proposed that assessment of main pancreatic duct (MPD) integrity by endoscopic retrograde pancreatography (ERP) could be used to determine the mode of intervention[16]. There is, however, little information on the state of the MPD during the natural history of acute pancreatitis and how this might relate to therapy.

This study reports the findings at ERP in 105 patients with acute pancreatitis in relation to outcome.

Patients and methods

A total of 105 consecutive patients who had undergone successful ERP during an attack of acute pancreatitis presenting to hospitals in Leicester and Dudley Road Hospital, Birmingham, in the 11 years to October 1991 were reviewed retrospectively.

The ERP findings were compared with prognostic criteria of severity, CT and clinical outcome. The diagnosis of acute pancreatitis was based on an admission serum amylase level >1000 units/l (Phadebas method; normal range 70–300 units/l) in the presence of a compatible clinical picture. The aetiology was established using previously described criteria[17]. The predicted severity of the attack was assessed using modified Glasgow criteria determined within 48 h of admission (*Table 1*). Complications were categorized as localized to

Table 1 *The modified Glasgow system used for prediction of severity*

Factors	
Age >55 years	P_{aO_2} < 8·0 kPa
White cell count >15 × 10^9/l	Albumin <32 g/l
Blood glucose >10 mmol/l	Calcium <2·0 mmol/l
Urea >16 mmol/l	Lactate dehydrogenase >600 units/l

Values were determined within 48 h of admission. P_{aO_2}, arterial partial pressure of oxygen. Predicted mild attack, 0–2 factors; predicted severe attack, 3–8 factors

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Based on a presentation to the Pancreatic Society of Great Britain and Ireland in Glasgow, UK, November 1991 and published in abstract form as Gut *1992;* **33**: *A426–8*

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the pancreas or systemic as previously described[17]. A pseudocyst was defined as a fluid collection arising from within the substance of the pancreas (in contrast to a peripancreatic fluid collection adjacent to or distant from the gland). Necrosis was classified as sterile or infected only if material was submitted for culture after debridement or percutaneous aspiration. An abscess was defined as a collection of pus.

Endoscopic retrograde cholangiopancreatography (ERCP) and contrast-enhanced CT were performed using standard techniques[18–20]. ERCP was used in the first 95 patients to determine the aetiology with a view to endoscopic sphincterotomy (ES) for gallstone-related pancreatitis[18] and in the last ten patients with the additional or sole purpose of examining the MPD. Similarly, CT was initially used as part of a prospective study[19] (50 examinations) and latterly in selected clinically severe cases[20] (ten examinations). The extent of necrosis determined on CT was assessed by a consultant radiologist. All patients had abdominal ultrasonography performed on admission and then serially as the clinical picture dictated.

Finally patients were divided into two groups for comparison of the ERP findings. Group 1 consisted of those with clinically mild pancreatitis or with a clinically severe attack but who did not require surgery for local complications; when available CT showed oedematous pancreatitis with <25 per cent necrosis. Group 2 consisted of patients with clinically severe pancreatitis who required surgery for localized complications, or who had ≥25 per cent pancreatic necrosis determined by CT, surgery or post mortem.

Results

There were 89 patients in group 1, all of whom were well on discharge (*Table 2*). There were nine patients with pseudocysts, which all resolved with conservative management. None of the pseudocysts showed direct communication with the MPD. Twenty-four patients underwent ES for bile duct stones. Eighteen patients (20 per cent) were hospitalized for ≥15 days (in two because of prophylactic cholecystectomy); nine of these had ≥3 prognostic factors (median for all 18 patients 2·5 (range 0–6)); age was median 78 (range 38–86) years; 15 had gallstones and three idiopathic pancreatitis. In none of the 89 patients was there evidence of MPD disruption. The duct often showed slight irregularities with blunting of side branches (*Figure 1*). There were no apparent complications after ERP.

There were 16 patients in group 2, three of whom were tertiary referrals (*Table 3*). The median age was 59 (range 26–85) years. Ten patients had gallstones, one cholesterolosis, one had polyarteritis nodosa and four an alcoholic aetiology. Four patients had ERP performed before 5 days after onset and all had non-disruption of the MPD (referred to as 'normal'

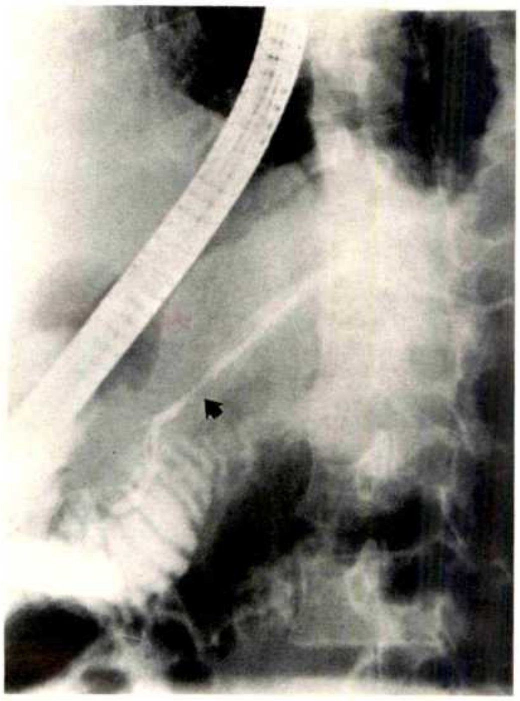

Figure 1 *Endoscopic pancreatography in a patient with oedematous pancreatitis shown by contrast-enhanced computed tomography. Note the blunting of side branches and irregularity and slight compression of the main pancreatic duct (arrow), especially in the head of the gland*

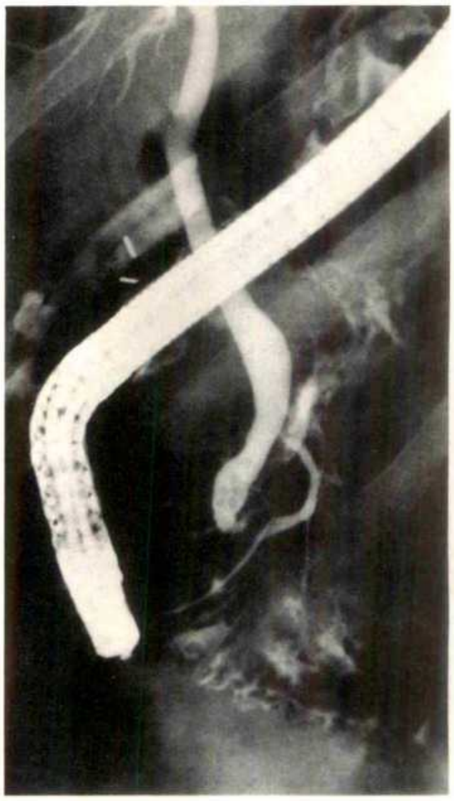

Figure 2 *Endoscopic retrograde pancreatography showing the main pancreatic duct to be completely disrupted in the head of the gland. The corresponding computed tomography image is shown in* Figure 3

Table 2 *Details of patients in group 1, with clinically mild pancreatitis or clinically severe pancreatitis but no surgery required and who had <25 per cent necrosis on computed tomography*

Aetiology	Sex ratio (M:F)	Age (years)*	Prognostic factors*	No. with ≥3 prognostic factors†	Interval to ERP (days)*	CT performed†	Complications†		Hospital stay (days)*
							Local	Systemic	
Gallstones ($n = 66$)‡	30:36	66 (23–88)	1·5 (0–6)	16	6 (0–30)	37	7§	2♯	10 (4–33)
Alcoholic ($n = 7$)	7:0	32 (20–46)	0 (0–3)	1	15 (0–20)	4	0	0	6 (4–16)
Idiopathic ($n = 16$)	8:8	56 (20–83)	1 (0–5)	3	5·5 (1–23)	7	2§	1¶	8 (5–26)
Total ($n = 89$)	45:44	63 (20–88)	1 (0–6)	20 (22)	6 (0–30)	48 (54)	9 (10)	3 (3)	9 (4–33)

*Values are median (range); †values in parentheses are percentages. ERP, endoscopic retrograde pancreatography; CT, computed tomography. ‡Twenty-four patients underwent endoscopic sphincterotomy including 12 who also had acute cholangitis; §all had pseudocysts but no active treatment was required; ♯one case each had cardiac failure and pseudo-obstruction; ¶respiratory failure

Table 3 *Details of patients in group 2 with clinically severe pancreatitis who required surgery for local complications and/or had ≥ 25 per cent necrosis on surgery, post mortem or computed tomography when performed*

Patient no.	Age (years)	Sex	Aetiology	Prognostic factors	Interval to ERP (days)	ERP finding*	Necrosis on CT (%)	Complication	Surgery	Post mortem	Hospital stay (days)
1	69	F	Gallstones	3	1	'Normal' MPD	25	Pseudocyst	Drainage of pseudocyst; minimal necrosis	—	16
2	53	F	Gallstones†‡	4	2	'Normal' MPD	Not performed	Multisystem failure; ascites; death	None	Extensive necrosis	3
3	75	M	Gallstones	3	2	'Normal' MPD	30	Pseudocyst	None	—	36
4	85	F	Gallstones	4	2	'Normal' MPD	30	Cardiac and respiratory failure; cerebrovascular accident; death	None	None	27
5	51	M	Gallstones‡	3	5	Disruption of MPD in head	50	Pseudocyst; infected necrosis	Necrosectomy; extensive necrosis	—	49
6	39	M	Alcoholic	5	8	'Normal' MPD	50	Pseudocyst; sterile necrosis; respiratory failure; cardiac failure	None	—	36
7	74	M	Gallstones†‡	4	14	'Normal' MPD	Not performed	Pseudocyst; respiratory failure	Drainage of pseudocyst; minimal necrosis	—	39
8	51	M	Polyarteritis nodosa	3	14	'Normal' MPD	30	Pseudocyst; respiratory failure	None	—	38
9	65	F	Gallstones	3	15	'Normal' MPD	25	Pseudocyst; respiratory failure	Drainage of pseudocyst; minimal necrosis	—	28
10	57	F	Gallstones‡	3	18	Multiple disruptions in body of MPD	Not performed	Necrosis; respiratory failure	Necrosectomy; extensive necrosis	—	32
11	73	F	Gallstones	4	22	Disruption of MPD in head	Not performed	Infected necrosis; pancreatic abscess; right subphrenic abscess; death	Necrosectomy; extensive necrosis	None	33
12	66	F	Alcoholic	4	24	Disruption of MPD in tail	25	Infected necrosis	Necrosectomy; necrosis in tail	—	44
13	44	M	Alcoholic	6	29	Disruption of MPD in head	95	Infected necrosis; septicaemia	Necrosectomy; extensive necrosis	—	108
14	61	M	Gallstones	5	30	'Normal' MPD	50	Duodenal obstruction; respiratory failure	None	—	43
15	41	M	Cholesterolosis	4	30	Disruption of MPD in head	90	Infected necrosis; pseudocyst; septicaemia	Necrosectomy; extensive necrosis	—	47
16	26	F	Alcoholic	5	35	Communicating pseudocyst; disruption of MPD in body	75	Infected necrosis; pseudocyst; septicaemia; ascites	Necrosectomy and distal pancreatectomy; extensive necrosis	—	60

ERP, endoscopic retrograde pancreatography; CT, computed tomography; MPD, main pancreatic duct. *'Normal' MPD refers to a non-disrupted duct; †accompanied by acute cholangitis; ‡endoscopic sphincterotomy performed

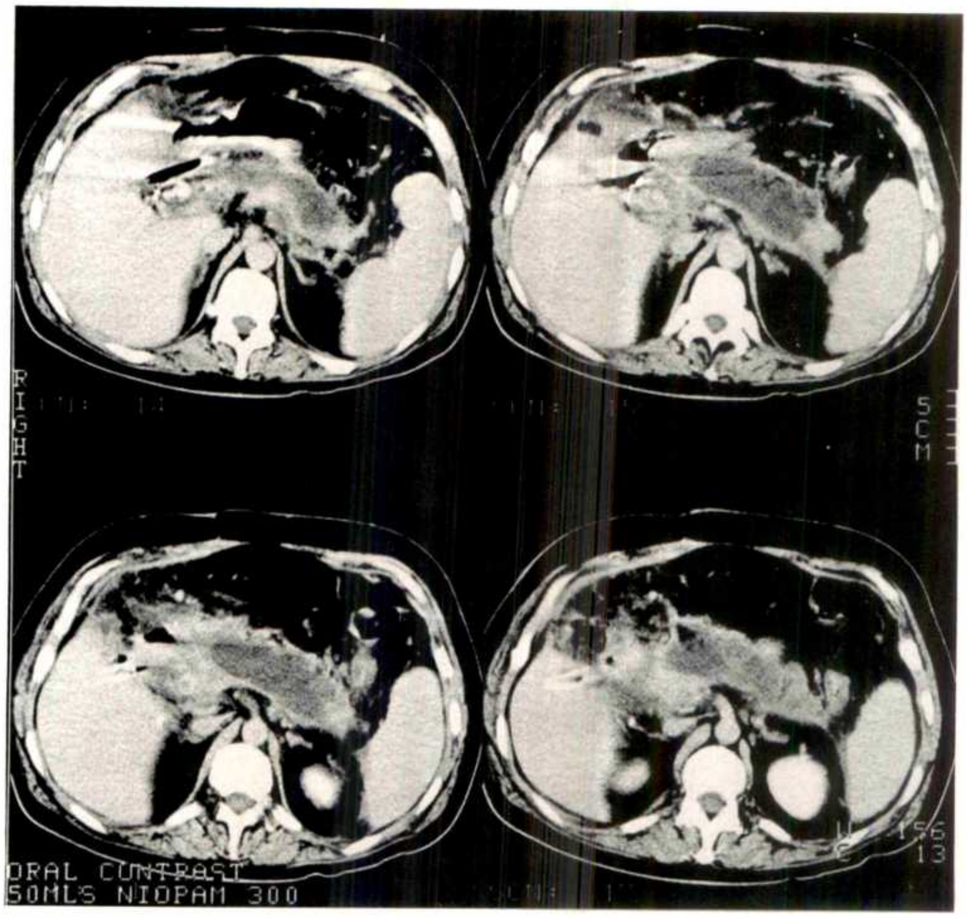

Figure 3 *Contrast-enhanced computed tomography suggesting 90 per cent necrosis with remnant activity in the tail of the pancreas (same patient as in* Figure 2*). The degree of necrosis was confirmed at surgery*

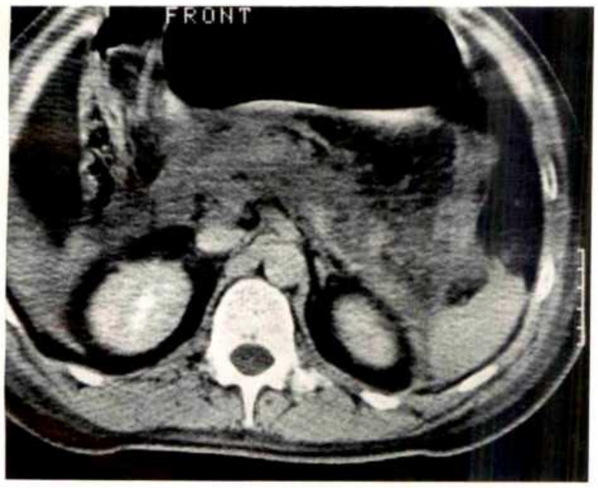

Figure 4 *Contrast-enhanced computed tomography suggesting 50 per cent necrosis; pancreatography revealed an intact pancreatic duct and percutaneous pancreatic aspirates confirmed necrosis but were negative on bacterial culture (sterile necrosis)*

in *Table 3*). Two patients died, one from extensive necrosis shown at post mortem and the other from a cerebrovascular accident (CT showed 30 per cent necrosis). Of the 12 patients in group 2 who had ERP performed 5 days or more after onset, seven had disruption in the head ($n = 4$), body ($n = 2$) or tail ($n = 1$) of the gland. All seven required necrosectomy, in six associated with infected necrosis (*Figures 2* and *3*), of whom one eventually died from septic complications. The organisms grown were always of gut origin. The species identified were *Escherichia coli*, *Streptococcus faecalis*, *S. mitis*, *Klebsiella* spp., *Pseudomonas mitis*, *Enterobacter cloacae* and *Enterobacter* spp.; in four cases one or more of these organisms were grown from blood cultures preceding ERP. In the remaining five patients in group 2 who had ERP performed at 5 days or later, the MPD was not disrupted; the extent of necrosis was 25–50 per cent but surgery was required in only two for pseudocyst drainage and there were no deaths. An example of CT suggesting extensive necrosis in a patient who was managed conservatively on the basis of sterile growth on percutaneous cytology and culture and a non-disrupted MPD is shown in *Figure 4*.

It should be noted that of nine patients with pseudocysts in group 2, in only one did this communicate with the MPD.

Discussion

Because this is largely a retrospective study, the data need to be interpreted with some caution. Nevertheless, there are a number of tentative conclusions that may be drawn. First, disruption of the MPD did not occur in clinically mild cases or in patients who did not require surgery for pancreatic necrosis. Pseudocysts, which occurred in nine patients in group 1, all resolved on conservative management.

Second, disruption of the MPD was not found within 5 days of onset of an attack of acute pancreatitis even though one patient died at 3 days with extensive necrosis. This observation should be balanced, however, by the fact that only four patients with necrosis had ERP within 5 days and also that the MPD was perhaps underfilled since the main purpose of ERCP in the early part of the study was identification of bile duct stones.

Third, this study suggests that MPD disruption may be more common than previously realized in extensive pancreatic necrosis as disruption of the duct was identified in seven of 16 patients (44 per cent). Moreover, all seven patients with a disrupted MPD required surgery for pancreatic necrosis.

There is surprisingly little information in the surgical literature regarding the state of the MPD in acute pancreatitis. Howard and Wagner[21] reported 12 patients who underwent ERP at 10 weeks to 23 months after an attack of 'massive' pancreatic necrosis requiring surgery, in which the MPD was essentially normal in ten cases. These authors, commenting on their overall surgical experience with 31 similar cases, noted that '... communication of the peri-pancreatic cavity with the pancreatic ductal system, over the course of the natural history of the disease, was seldom demonstrable'.

Gebhardt *et al.* in their initial report[16] described four different features of ERP along with morphological findings and with different surgical strategies in eight patients who required surgery on the basis of clinical criteria. These were: (1) normal MPD, associated with peripancreatitis only, treated by isolated necrosectomy; (2) isolated MPD disruption associated with peripancreatitis with an isolated fistula, treated by left resection of the pancreas including the fistula; (3) diffuse parenchymal staining, associated with total necrosis, treated by left resection of the pancreas; and (4) disruption in the head of the gland with necrosis perforation into the medial wall of the duodenum, treated conservatively.

On the basis of ERP in an expanded series of 42 patients from Erlangen[22,23], three (7 per cent) were treated conservatively, 17 (40 per cent) by necrosectomy and 22 (52 per cent) by resection plus necrosectomy. Deaths occurred in six (14 per cent) of these patients compared with 31 of 89 (35 per cent) treated by necrosectomy without the benefit of ERP in the period immediately preceding its introduction. It is noteworthy that much of the experience of the Erlangen group did not involve the use of contrast-enhanced CT and in the latter part necrosectomy was combined with lavage.

In the present study necrosectomy was routinely used with drainage or lavage and only one formal resection (in combination with necrosectomy) was undertaken. The experience of the present authors, although more limited than that of the Erlangen group, indicates that necrosectomy may be a satisfactory alternative to resection in cases of MPD disruption.

Serum markers of severity are not always accurate indicators for surgical intervention[24], and while contrast-enhanced CT is accurate in determining the extent of necrosis, this does not always correlate with disease severity or clinical outcome[20,25]. Although it is generally agreed that contrast-enhanced CT greatly facilitates planning and execution of surgery, many authors now stress that a CT finding of necrosis in patients with severe pancreatitis is not of itself an indication for operation[26–29]. Even the notion that infected necrosis is associated with a worse prognosis[30] has been challenged by a recent study[31] in which there was no difference in outcome between patients with sterile *versus* infected necrosis.

The inadequacy of present diagnostic methods for a number of patients demands the development of additional techniques. It is conceivable that disruption of the MPD might prove to be an indicator for intervention as suggested by existing, albeit anecdotal, evidence[32,33]. However, there is some concern that ERP may introduce infection into the pancreas. In the present study, four of six patients with infected necrosis had the same organisms grown from the blood before ERCP. In two randomized trials[17,34] of ERCP in gallstone pancreatitis, containing 283 patients, there was no evidence of an increased incidence of complications. Collectively over 1000 patients with acute pancreatitis have undergone ERCP with a mortality rate <2 per cent and morbidity rate <6 per cent[35]. Nevertheless, it must be stressed that ERP in severe acute pancreatitis must be undertaken by a skilled endoscopist in association with a specialist surgical unit and that the patient must be receiving systemic broad-spectrum antibiotics. In considering the pathogenesis of local necrosis and pancreatic pseudocyst, a distinction should be made between a pseudocyst communicating with the MPD during acute pancreatitis and duct disruption with parenchymal staining by contrast as shown by ERP. A communicating pseudocyst in acute pancreatitis is rare, as compared with either acute on chronic, or chronic, pancreatitis[36]. In the present study, only one of 18 pseudocysts (6 per cent) communicated with the MPD and this was quite separate from extravasation into the parenchyma. CT in association with ERP is required to make an accurate evaluation.

In conclusion, the integrity of the MPD seems to be maintained in mild pancreatitis. Significant peripancreatic necrosis may occur in association with an intact duct, although surgery is only sometimes indicated. In the present series, disruption of the MPD was always associated with extensive necrosis that required surgical intervention.

Any future clinical role for ERP in the management of necrotizing pancreatitis will need to be determined by further prospective study.

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References

1. Wilson C, McArdle CS, Carter DC, Imrie CW. Surgical treatment of acute necrotizing pancreatitis. *Br J Surg* 1988; **75**: 1119–23.
2. Winslet M, Hall C, London NJM, Neoptolemos JP. Sensitivity of diagnostic serum amylase levels: relationship to aetiology and severity. *Gut* 1992; **33**: 982–6.
3. D'Egidio A, Schein M. Surgical strategies in the treatment of pancreatic necrosis and infection. *Br J Surg* 1991; **78**: 133–7.
4. Allardyce DB. Incidence of necrotizing pancreatitis and factors related to mortality. *Am J Surg* 1987; **154**: 295–9.
5. Bradley EL III, Allen K. A prospective longitudinal study of observation *versus* surgical intervention in the management of necrotizing pancreatitis. *Am J Surg* 1991; **161**: 19–25.
6. Sarr MG, Nagorney DM, Mucha P, Farnell MB, Johnson CD. Acute necrotizing pancreatitis: management by planned staged pancreatic necrosectomy/debridement and delayed primary wound closure over drains. *Br J Surg* 1991; **78**: 576–81.
7. Beger HG, Buchler M, Bittner R, Block S, Nevalainen T, Roscher R. Necrosectomy and postoperative local lavage in necrotizing pancreatitis. *Br J Surg* 1988; **75**: 207–12.
8. Pederzoli P, Rassi C, Vesentini S *et al.* Necrosectomy by lavage in the surgical treatment of severe necrotizing pancreatitis. *Acta Chirurgica Scandinavica* 1990; **156**: 775–80.
9. Freeny PC, Lewis GP, Traverso LW, Ryan JA. Infected pancreatic fluid collections: percutaneous catheter drainage. *Radiology* 1988; **167**: 435–41.
10. Adams DB, Harvey TS, Anderson MC. Percutaneous catheter drainage of infected pancreatic and peripancreatic fluid collections. *Arch Surg* 1990; **125**: 1554–7.
11. Poston GJ, Williamson RCN. Surgical management of acute pancreatitis. *Br J Surg* 1990; **77**: 5–12.
12. Block S, Maier W, Bittner R, Buchler M, Malfertheiner P, Beger HG. Identification of pancreas necrosis in severe acute pancreatitis: imaging procedures *versus* clinical staging. *Gut* 1986; **27**: 1035–42.
13. Larvin M, McMahon MJ. APACHE-II score for assessment and monitoring of acute pancreatitis. *Lancet* 1989; **ii**: 201–5.
14. Buchler M, Malfertheiner P, Sheoetensack C, Uhl W, Beger HG. Sensitivity of antiproteases, complement factors and C-reactive protein in detecting pancreatic necrosis. Results of a prospective clinical study. *Int J Pancreatol* 1986; **1**: 227–35.
15. Buchler M, Malfertheiner P, Schadlich H, Nevalainen TJ, Freiss H, Beger HG. Role of phospholipase A_2 in human acute pancreatitis. *Gastroenterology* 1989; **97**: 1521–6.
16. Gebhardt CH, Riemann JF, Lux G. The importance of ERCP for the surgical tactic in haemorrhagic necrotizing pancreatitis. (Preliminary report.) *Endoscopy* 1983; **15**: 55–8.
17. Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA,

James D, Fossard DP. Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy *versus* conservative treatment for acute pancreatitis due to gallstones. *Lancet* 1988; **ii**: 979–83.

18. Neoptolemos JP, Carr-Locke DL, London N, Bailey I, Fossard DP. ERCP findings and the role of endoscopic sphincterotomy in acute gallstone pancreatitis. *Br J Surg* 1988; **75**: 954–60.
19. London NJM, Neoptolemos JP, Lavelle J, Bailey I, James D. Serial computed tomography scanning in acute pancreatitis: a prospective study. *Gut* 1989; **30**: 397–403.
20. London NJM, Leese T, Lavelle JM *et al.* Rapid-bolus contrast-enhanced dynamic computed tomography in acute pancreatitis: a prospective study. *Br J Surg* 1991; **78**: 1452–6.
21. Howard JM, Wagner SM. Pancreatography after recovery from massive pancreatic necrosis. *Ann Surg* 1989; **209**: 31–5.
22. Gebhardt C. Indications for surgical intervention in necrotizing pancreatitis with extrapancreatic necrosis. In: Beger HG, Buchler M, eds. *Acute Pancreatitis*. Berlin: Springer-Verlag, 1987: 310–13.
23. Meister R. Treatment of biliary pancreatitis: approach, technique and results. In: Beger HG, Buchler M, eds. *Acute Pancreatitis*. Berlin: Springer-Verlag, 1987: 251–6.
24. Ferguson CM, Bradley EL. Can markers for pancreatic necrosis be used as indicators for surgery? *Am J Surg* 1990; **160**: 459–61.
25. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JHC. Acute pancreatitis: value of CT in establishing prognosis. *Radiology* 1990; **174**: 331–6.
26. Larvin M, Chalmers AG, McMahon MJ. Dynamic contrast-enhanced computed tomography: a precise technique for identifying and localising pancreatic necrosis. *BMJ* 1990; **300**: 1425–8.
27. Bradley EL, Murphy E, Ferguson C. Prediction of pancreatic necrosis by dynamic pancreatography. *Ann Surg* 1989; **210**: 495–503.
28. Testas P, Abittan R, Chollet JM, Benichou J, Cauomil P. On the utilization of CT-scanning during the initial phase of acute pancreatitis. *Chirurgie* 1988; **114**: 785–9.
29. Kummerle F. Clinical staging in acute pancreatitis. In: Beger HG, Buchler M, eds. *Acute Pancreatitis*. Berlin: Springer-Verlag, 1987: 177–80.
30. Beger HG, Bittner R, Block S, Buchler M. Bacterial contamination of pancreatic necrosis. A prospective clinical study. *Gastroenterology* 1986; **91**: 433–8.
31. Rattner DW, Legermane DA, Lee MJ, Mueller PR, Warshaw AL. Early surgical debridement of symptomatic pancreatic necrosis is beneficial irrespective of infection. *Am J Surg* 1992; **163**: 105–9.
32. Nordback I, Airo I. ERCP demonstration of pancreatic sequester after necrotizing pancreatitis. *Surgical Research Communications* 1988; **4**: 87–91.
33. Bradley EL. Open packing for infected pancreatic necrosis. In: Beger HG, Buchler M, eds. *Standards of Pancreatic Surgery*. Berlin: Springer-Verlag, 1992 (in press).
34. Nowak A, Nowakowska-Duzawa E, Rybicka J. Urgent endoscopic sphincterotomy *vs* conservative treatment in acute biliary pancreatitis – a prospective, controlled trial. *Hepatogastroenterology* 1990; **37**(Suppl II): A5.
35. Neoptolemos JP, Stonelake P, Radley S. Endoscopic sphincterotomy for acute pancreatitis. *Hepatogastroenterology* 1993 (in press).
36. D'Egido A, Schein M. Pancreatic pseudocysts: a proposed classification and its management implications. *Br J Surg* 1991; **78**: 981–4.

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Long-term follow-up after open cholecystectomy

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The long-term outcome of open cholecystectomy was investigated. Follow-up data at a median of 10 years were obtained from physicians' records on 325 (92·6 per cent) of 351 patients treated for symptomatic gallbladder stones by open cholecystectomy between 1978 and 1980. One 79-year-old patient died after operation, from a pulmonary complication. Of the 325 patients, 81·5 per cent were currently asymptomatic or had not had symptoms during follow-up until death. Sixty patients (18·5 per cent) had complaints after 10 years. Stone recurrence was found in five patients (1·5 per cent); ten others (3·1 per cent) had biliary tract-related complaints during follow-up. Blood samples were obtained in 67·3 per cent of surviving patients with biliary complaints. There were no laboratory findings associated with biliary obstruction. Patients with typical symptoms of gallstone disease before surgery had significantly fewer complaints during follow-up than those with typical as well as atypical symptoms (14·8 versus *26·5 per cent,* $P < 0·02$*). However, most of these complaints were not related to the procedure. It is concluded that the majority of patients reported no complaints or postcholecystectomy symptoms 10 years after surgery.*

Cholecystectomy is still the 'gold standard' for the treatment of symptomatic gallstones, especially after the introduction of the laparoscopic technique[1,2]. However, postcholecystectomy symptoms have been reported[3,4] in 12–47 per cent of patients in follow-up periods ranging from 24 to 45 months. Follow-up in most studies of open cholecystectomy has been short, and such reports have been restricted mostly to a limited number of patients[3–6]. The number of patients suffering from postcholecystectomy symptoms and recurrent gallstone disease during prolonged follow-up is unknown. It has been suggested on the basis of a prospective study that a relationship exists between preoperative symptoms such as dyspepsia and outcome after surgery[3]. In contrast, a more recent cohort study did not confirm this[5]. The present study therefore evaluated complaints 10 years after conventional cholecystectomy and attempted to relate these to preoperative symptoms.

Patients and methods

Patients

Surgery for gallstone disease was performed on 490 patients during 1978–1980. Open cholecystectomy was carried out in 351 (263 female and 88 male) patients. During this period another 139 patients underwent cholecystectomy and exploration of the common bile duct (CBD) for bile duct stones. These patients have been excluded from this study.

Clinical assessment

The medical records of all 351 patients were reviewed. Their median age at the time of operation was 56 (range 17–87) years; 128 were older than 60 years. Emphasis was put on the study of symptoms before surgery, patients being divided into two groups on the basis of symptoms recorded before operation. Patients in group 1 ($n = 244$; 69·5 per cent) had symptoms typical of gallstone disease, such as colicky pain in the right upper quadrant of the abdomen, in accordance with the Roma working group report[7].

Patients in group 2 ($n = 107$; 30·5 per cent) displayed complaints typical of gallstone disease and in addition atypical symptoms such as heartburn, indigestion, flatulence, gastritis and/or symptoms of gastro-oesophageal reflux disease (*Table 1*). All patients underwent conventional open cholecystectomy. Peroperative cholangiography to exclude bile duct stones was performed routinely. Cholecystectomy was performed at the time of presentation with acute symptoms in 45 patients (12·8 per cent) and as an elective procedure in 306 (87·2 per cent).

Table 1 *Symptoms recorded in 351 patients before cholecystectomy*

	Group 1* ($n = 244$)	Group 2† ($n = 107$)	Total ($n = 351$)
History of recurrent jaundice	24 (9·8)	8 (7·5)	32 (9·1)
Right upper quadrant pain	223 (91·4)	72 (67·3)	295 (84·0)
Biliary colic	144 (59·0)	45 (42·1)	189 (53·8)
Postprandial pain	116 (47·5)	48 (44·9)	164 (46·7)
Nausea	127 (52·0)	57 (53·3)	184 (52·4)
Dyspepsia	0 (0)	16 (15·0)	16 (4·6)
Heartburn	0 (0)	46 (43·0)	46 (13·1)
Gastritis	0 (0)	24 (22·4)	24 (6·8)
Symptomatic gastro-oesophageal reflux	0 (0)	40 (37·4)	40 (11·4)

Values in parentheses are percentages. *Patients in group 1 had only typical symptoms before cholecystectomy; †those in group 2 had typical and atypical symptoms before surgery

Table 2 *Symptom questionnaire*

Recurrent stones	Yes/no
Colicky pain in right upper quadrant	Yes/no
Jaundice	Yes/no
Cholangitis	Yes/no
Pancreatitis	Yes/no
Diarrhoea	Yes/no
Dyspepsia	Yes/no
Scar pain	Yes/no
Incisional hernia	Yes/no
Gastritis	Yes/no
Ulcer disease	Yes/no
Gastro-oesophageal reflux disease	Yes/no
Irritable bowel disease	Yes/no
Cause and date of death where relevant	

The general practitioner of every patient was asked to record whether or not each symptom had been reported by the patient after surgery

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Table 3 *Symptoms recorded in 325 patients at 10-year follow-up after cholecystectomy*

Group*	No.	Symptom-free	Symptoms†	Biliary tract-related	Laparotomy wound-related	Atypical symptoms
1	223	190 (85·2)	33 (14·8)	7 (3·1)	2 (0·9)	24 (10·8)
2	102	75 (73·5)	27 (26·5)	8 (7·8)	2 (2·0)	17 (16·7)
Total	325	265 (81·5)	60 (18·5)	15 (4·6)	4 (1·2)	41 (12·6)

Values in parentheses are percentages. *Patients in group 1 had typical symptoms before cholecystectomy; those in group 2 had typical and atypical symptoms before surgery. †There were significantly more complaints in group 2 ($\chi^2 = 5{\cdot}58$, 1 d.f., $P = 0{\cdot}018$)

Follow-up

Relief of symptoms was studied by sending questionnaires to the general practitioners (GPs) of 291 patients (*Table 2*). If a patient's GP could not be contacted, the questionnaire was sent to the patient and he or she was telephoned afterwards (replies received from 34). Follow-up covered a median of 10 years (range 4 months to 12 years) and was complete in 325 patients (92·6 per cent). The questions covered biliary tract symptoms, wound-related problems (hernia or scar pain) and atypical symptoms such as gastro-oesophageal reflux disease, gastritis and peptic ulcer. Blood samples were taken from surviving symptomatic patients for estimation of alkaline phosphatase, γ-glutamyl transferase, glutamic–pyruvic transaminase and serum bilirubin.

Results

Clinical assessment

Preoperative symptoms are shown in *Table 1*. One 79-year-old patient died after surgery from a pulmonary complication. Procedure-related complications such as bile leakage from a drain ($n = 3$), wound abscess ($n = 4$) and wound infection ($n = 12$) developed in 19 patients (5·4 per cent); other complications such as cardiac failure ($n = 4$), pulmonary infection ($n = 12$) and/or urinary tract infection ($n = 11$) were found in 27 patients (7·7 per cent).

Follow-up

Some 78 patients died after a median follow-up of 6 years (range 4 months to 12 years). Eight of these patients had complaints before death and six suffered from symptoms suggestive of gallstone disease, although none was found to have residual stones. One of these patients underwent laparotomy and CBD exploration 4 years before death, but no abnormality was found. This patient later died from a myocardial infarction. Another patient suffered an episode of cholangitis, which was adequately treated with antibiotics, but the cause of death was in this case unknown. Two of the remaining four patients with complaints died from malignant disease; the other two died from cardiac disease. Two patients had had atypical complaints before death, but the cause of this was not associated with previous surgery for gallstone disease.

At the time of the study 247 patients were alive. Fifty-two (21·1 per cent) of these had experienced complaints at some time after cholecystectomy or still have them at present. Nine patients had biliary tract symptoms; bile duct stones were found in five of these. Stones were treated endoscopically in three patients. The other two underwent CBD exploration resulting in stone removal. Four patients had laparotomy wound-related problems such as hernias ($n = 2$) or scar pain ($n = 2$) and 39 had atypical symptoms.

Blood samples were obtained from 35 of the 52 surviving symptomatic patients. Four patients showed raised levels of at least one liver function assay. Recurrent or new bile duct stones could not be completely excluded in these four patients, although the pattern of laboratory results made recurrent CBD stones unlikely.

The relationship between preoperative symptoms and complaints during follow-up in the 325 patients is shown in *Table 3*. The 102 patients with a combination of typical and atypical preoperative symptoms (group 2) suffered proportionately more complaints (26·5 per cent) than the 223 with typical symptoms before surgery (group 1) (14·8 per cent). No other significant association was found between preoperative findings (such as age, sex and indication for operation) and complaints during follow-up.

Discussion

This series achieved a nearly complete follow-up (92·6 per cent) of the original treatment group 10 years after cholecystectomy. This high percentage is the result of geographical circumstances and probably the fact that the questionnaire was sent to patients' GPs. However, the present study differs from others in that it investigates only symptoms described before operation in the case records, and postoperative symptoms reported by the patient to their GP. The latter may have led to under-recording of postoperative symptoms.

Regarding the relatively high proportion of postoperative complications (13·1 per cent) in the original 351 patients undergoing surgery it should be noted that these patients were operated on 10 years ago. The high proportion (28·4 per cent) of patients undergoing cholecystectomy and CBD exploration in this series might be because endoscopic retrograde cholangiography and endoscopic sphincterotomy were not available at that time. Operative cholangiography was performed routinely and, in case of doubt about the presence of CBD stones, bile duct exploration was undertaken.

Of the patients who were followed up, 81·5 per cent did not consult their GP with abdominal symptoms related to previous gallstone disease during the 10 years after cholecystectomy. Sixty patients (18·5 per cent) remained symptomatic. This is lower than the numbers reported by other authors, although this may reflect differences in methodology[3–5,8]. Bile duct stones were found in five patients (1·5 per cent) and four other survivors showed symptoms that may have been associated with biliary tract disease, although blood samples in these symptomatic patients did not support a diagnosis of CBD stones. However, this does not exclude sphincter dysfunction in these patients. New bile duct stones have been reported[3,4] at a rate of 0–1 per cent. It is therefore concluded that the percentage of recurrent gallstones does not increase during 10-year follow-up.

Forty-one patients (12·6 per cent) were found to have symptoms that were not typical of biliary disease 10 years after surgery. Atypical symptoms have been observed in previous studies[3–5,8] in 12–47 per cent of patients after open cholecystectomy, with a mean follow-up ranging from 2 to 4 years. The proportion with atypical symptoms in the present study (12·6 per cent) is lower than the 47 per cent in a recent prospective report[4]; this might be due to the retrospective nature of the present analysis and to differences related to the source of the information (patient or GP). Atypical symptoms were investigated in the questionnaire, but these were recorded by GPs for only 12·6 per cent of patients.

It is possible that the outcome after surgery could be improved if patients were carefully selected for operation. Despite the inherent difficulty of a retrospective analysis of symptoms from case records, it was found that patients with typical biliary symptoms before operation developed significantly fewer complaints (14·8 per cent) than those who also showed atypical preoperative symptoms (26·5 per cent). Further work is necessary in a prospective study to clarify the relationship between symptoms before surgery and outcome afterwards.

Postcholecystectomy symptoms after the newer treatments for symptomatic gallstones such as laparoscopic cholecystectomy, which is becoming the treatment of choice for this condition[9], will probably be similar to those after the open operation because the gallbladder is also removed. Complaints such as incisional hernia and postoperative wound pain may be reduced[10], but these occur in only 1·2 per cent of patients. Symptoms before surgery (typical and atypical of biliary disease) may help to determine the final outcome, as the present results and other studies[3] of conventional cholecystectomy suggest. It seems likely that preoperative symptoms such as dyspepsia will persist after surgery[5], but further study is needed.

In conclusion, in this retrospective study of the long-term outcome of open cholecystectomy, the majority of patients had not presented with any abdominal symptoms 10 years after surgery. Postcholecystectomy symptoms were mostly atypical and not related to biliary tract disorders.

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References

1. McSherry CK. Cholecystectomy: the gold standard. *Am J Surg* 1989; **158**: 174–8.
2. Cuschieri A, Dubois F, Mouiel J *et al.* The European experience with laparoscopic cholecystectomy. *Am J Surg* 1991; **161**: 385–7.
3. Gilliland TM, Traverso LW. Modern standards for comparison of cholecystectomy with alternative treatment for symptomatic cholelithiasis with emphasis on long term relief of symptoms. *Surg Gynecol Obstet* 1990; **170**: 39–44.
4. Ros E, Zambon D. Postcholecystectomy symptoms. A prospective study of gall stone patients before and two years after surgery. *Gut* 1987; **28**: 1500–4.
5. Bates T, Ebbs SR, Harrison M, A'Hern RP. Influence of cholecystectomy on symptoms. *Br J Surg* 1991; **78**: 964–7.
6. Lee SH, Burhenne HJ. Persistence of symptoms after gallbladder clearance with cholelithotripsy. *Gut* 1991; **32**: 536–8.
7. Schönfield LJ, Carulli N, Dowling RH *et al.* Roma 88 working team rapportage. *Gastroenterology International* 1988; **1**: 17–24.
8. Bodvall B, Övergaard B. Computer analysis of postcholecystectomy biliary tract symptoms. *Surg Gynecol Obstet* 1967; **124**: 723–32.
9. Sauerbruch T, Paumgartner G. Gallbladder stones: management. *Lancet* 1991; **338**: 1121–4.
10. Cheslyn-Curtis S, Russell RCG. New trends in gallstone management. *Br J Surg* 1991; **78**: 143–9.

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Minimally invasive treatment for common bile duct stones

The impact of endoscopic surgery on the management of stones in the common bile duct (CBD) was studied. All patients with proven common duct stones managed by a single consultant during a 21-month period were included. Of a total of 60 patients, 48 were referred because of symptoms or signs of calculi in the CBD and 12 were found to have common duct stones although symptoms were related primarily to the gallbladder. Of the 48 patients referred with common duct stones, 41 (85 per cent) were successfully treated by endoscopic retrograde cholangiography (ERC) and endoscopic sphincterotomy (ES) (complications were cholangitis (one patient), mild acute pancreatitis (one), impacted retrieval basket (one)). Of the remaining seven patients, two underwent open exploration (one after failed laparoscopic exploration) and five had successful laparoscopic duct exploration. One patient underwent laparoscopic exploration of the CBD but subsequently died. Of the patients with primary gallbladder symptoms, eight underwent preoperative ES, one was treated by laparoscopic duct exploration, one by conversion to open operation and in two patients duct stones were removed at postoperative ERC. The overall mortality rate was 2 per cent and the incidence of complications 12 per cent. Open exploration of the CBD was performed in three patients (5 per cent). This experience suggests that open duct exploration will become increasingly infrequent and may be replaced by endoscopic surgery in the majority of patients.

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There has recently been a revolution in the management of gallstones. A spectrum of minimally invasive procedures has brought into question the traditional approaches to both cholecystolithiasis and choledocholithiasis. Laparoscopic cholecystectomy in the eyes of many is now the treatment of choice for cholecystolithiasis. In the hands of an experienced surgeon it is both safe and applicable to more than 95 per cent of patients with symptomatic gallstones[1].

The success of laparoscopic cholecystectomy has brought into focus problems with the management of duct stones, including those that present primarily with jaundice, pancreatitis or cholangitis and those found incidentally (secondarily) during the investigation or treatment of a patient with symptomatic gallbladder stones[2].

Should the traditional approach of open operation and common bile duct (CBD) exploration be followed? How should the patient discovered to have duct stones during the course of laparoscopic cholecystectomy be managed? Can a policy of preoperative endoscopic retrograde cholangiography (ERC) in selected patients, coupled with intraoperative cholangiography at laparoscopic cholecystectomy, produce results comparable to those previously reported with open operation? Finally, will laparoscopic duct exploration provide a direct minimally invasive replacement for open duct exploration?

In an attempt to answer some of these questions, a minimally invasive approach has been applied to the treatment of all patients with CBD stones who presented to one surgeon (M.J.McM.) during a 21-month period. During this period, with four exceptions, all patients who required surgery for gallbladder stones were offered laparoscopic cholecystectomy.

The protocol described below represents the management policy at the beginning of the study period. With the increasing realization that laparoscopic duct exploration was a viable and useful tool, the approach to CBD stones in this unit is changing rapidly and it is envisaged that in the next 1–2 years the relative emphasis of endoscopic sphincterotomy (ES) and laparoscopic duct exploration will be reversed.

Patients and methods

Treatment protocol

This report embraces all cases of choledocholithiasis managed by one surgeon since laparoscopic cholecystectomy was introduced as the routine management for gallbladder stones in June 1990. Patients were divided into two groups according to presentation of the CBD calculi.

Primary presentation. This group included patients who presented with symptoms or signs such as jaundice believed to be caused by a stone in the CBD. Endoscopic stone clearance was the initial treatment in this group and surgical or laparoscopic exploration of the bile duct was used only when endoscopic methods failed. Laparoscopic cholecystectomy was carried out only when indicated for symptoms related to the gallbladder. Open operation was used early in the series before increasing experience with laparoscopic surgery enabled laparoscopic duct exploration to be offered as the method of choice.

Secondary presentation. The presenting symptoms in this group of patients were related to stones in the gallbladder. Choledocholithiasis was identified in this group as a result of preoperative investigations or by operative cholangiography. Before laparoscopic cholecystectomy, ERC was carried out if one or more of the following criteria were satisfied: history of recent jaundice; raised liver enzyme levels; or dilatation of the CBD on ultrasonography.

The treatment policy in this group was to remove identified stones before operation by endoscopic stone clearance 1 day before laparoscopic cholecystectomy. If this was unsuccessful the patient underwent duct exploration using laparoscopic techniques (open operation was used in the first few months of the study and in one emergency case).

When duct stones were identified by operative cholangiography a decision was made to explore the duct at that operation or to proceed to ERC and endoscopic stone clearance about 3 weeks later. This decision was based on the age and health of the patient; if the patient

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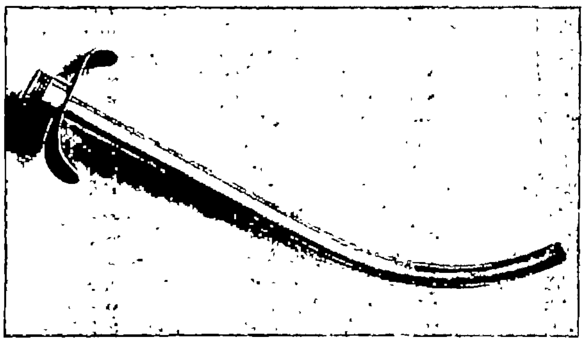

Figure 1 *The curved choledochoscope introducer used during laparoscopic duct exploration*

Table 1 *Details of patients with common duct stones*

	Primary symptoms of duct stones (*n* = 48)	Secondarily detected duct stones (*n* = 12)
Sex ratio (M:F)	17:31	2:10
Median (range) age (years)	56 (24–90)	52 (40–91)
Presentation		
Jaundice	43	0
Pancreatitis	5	0
Biliary colic	0	10
Cholecystitis	0	11
Raised liver enzyme levels	0	4
Management		
Endoscopic clearance	41 (85)	8 (67)
Laparoscopic clearance	5 (10)	1 (8)
Open duct exploration	2 (4)	1 (8)
Postoperative endoscopic retrograde cholangiography	0 (0)	2 (17)

Values in parentheses are percentages

was considered sufficiently fit to continue the anaesthetic then the duct was explored laparoscopically. Only in the elderly or infirm patient was delayed ES and duct clearance used.

Technique of endoscopic stone clearance

ERC was carried out in a routine manner. After sphincterotomy, stone clearance was carried out using retrieval baskets and balloons. If stones were large, the basket was exchanged for a mechanical lithotriptor. Nasobiliary drainage, mono-octanoin infusion and extracorporeal shockwave lithotripsy (ESWL) were used for large calculi resistant to mechanical lithotripsy.

Difficulty with access to the CBD for initial cannulation or subsequent sphincterotomy was overcome by needle-knife sphincterotomy[3].

Technique of laparoscopic exploration of the bile duct

Four routine cannulation sites for laparoscopic cholecystectomy were used[1]. If the gallbladder was present a catgut sling was passed around the cystic duct from the exterior to elevate this duct and keep it under tension. Small CBD stones were removed by a basket passed into the common duct through a transverse incision in the cystic duct under radiographic screening. Most small stones can be removed this way without the need for choledochotomy. With the use of sequential dilators passed through the cystic duct, a flexible choledochoscope can be introduced into the common duct[4]. The disadvantage of this technique is that the choledochoscope can be passed only into the CBD and not into hepatic ducts.

For larger stones and those within the biliary tree proximal to the junction of the cystic and common hepatic ducts, a longitudinal choledochotomy was made using a neodymium yttrium–aluminium–garnet laser (Surgical Laser Technologies, Malvern, Pennsylvania, USA) and the calculi removed using a 5-mm choledochoscope (Pentax; Ashai Optical Company, Tokyo, Japan). Manipulation of the choledochoscope using a laparoscopic forceps is likely to damage the coating of the flexible portion of the instrument and a curved introduction cannula (Surgical Innovations, Leeds, UK) is now employed (*Figure 1*). Large stones were fragmented using a 5-Fr electrohydraulic lithotriptor probe passed down the instrument channel of the endoscope (Richard Wolf Instruments, Tuttlingen, Germany). The remaining small fragments were removed by a combination of balloons and baskets passed through the choledochoscope. All ducts were visualized using the choledochoscope at the end of the procedure to ensure complete clearance.

Patients

The patient population for this study comprised two groups: those whose clinical problem was related directly to CBD stones and those whose primary problem was cholecystolithiasis and whose duct stones were discovered incidentally.

The details of 48 patients who presented with primary duct stones are shown in *Table 1*. All underwent ES initially.

During the study period 211 patients were listed for cholecystectomy. A total of 207 underwent laparoscopic cholecystectomy; four patients did not undergo laparoscopic surgery: one was considered unfit for general anaesthesia and three required concomitant open procedures (none of these patients had CBD stones).

Results

Primary symptoms of common duct stones

There were 48 patients with primary symptoms of CBD stones. All initially underwent ES and attempted endoscopic duct clearance. Successful duct clearance was achieved in 41 (85 per cent). There were two complications of successful ES: mild acute pancreatitis and a short-lived episode of cholangitis. Both responded to conservative medical therapy and were without sequel. There were no deaths in this group of patients who had endoscopic duct clearance, from either the ERC or subsequent surgery.

ERC was unsuccessful in seven patients, one of whom also had an episode of cholangitis. In one the stone extraction basket became impacted within the CBD and, as the mechanical lithotriptor was not available, emergency laparotomy was required. In the remaining six the stones could not be cleared from the duct and the patients proceeded to laparoscopic duct exploration, five in conjunction with cholecystectomy, on an elective basis.

There was one death (2 per cent) following laparoscopic duct exploration. This was a 71-year-old woman with multiple medical problems in whom ERC and ESWL had failed to clear the common duct stones. She underwent laparoscopic exploration of the CBD but died from cardiac failure 3 days later; the operation was technically uneventful and autopsy showed no intra-abdominal pathology. In one patient, laparoscopic duct exploration was abandoned owing to equipment failure; an uneventful open operation was performed. In the remaining five the duct was successfully cleared of stones, a finding confirmed by choledochoscopy (83 per cent successful duct clearance rate). Five of these six patients were explored through a choledochotomy because large stones were present. One of these five patients had undergone previous open CBD exploration.

Secondarily detected common duct stones

A total of 207 patients underwent laparoscopic cholecystectomy, including 18 who had presented with primary duct calculi. There were no deaths and there were two conversions to open operation. Thirty-three of the 189 patients who presented with symptoms related to the gallbladder underwent preoperative ERC, the indication being previous jaundice in ten, a dilated CBD in eight and abnormal liver function test results in 17. Of the 156 patients who did not undergo preoperative ERC, 95 underwent successful intraoperative cholangiography. The reason for failure to obtain a successful cholangiogram was usually the presence of a very small cystic duct that would not allow introduction of the cholangiography catheter. In these circumstances cholangiography was not vigorously pursued because it was felt unlikely that any significant stones could have entered the common duct.

Twelve patients with secondarily detected CBD stones were identified. Eight were recognized at preoperative ERC, all of whom were managed successfully by endoscopic duct clearance without complication. Four patients with duct stones were identified at intraoperative cholangiography. One underwent conversion to open duct exploration, one had successful laparoscopic CBD exploration through the cystic duct and in two elderly patients duct stones were cleared at postoperative ERC.

Of the four patients whose duct stones were discovered at operative cholangiography, three were known to have a dilated CBD before operation; of the 156 patients in whom there was no indication for preoperative ERC, only one was subsequently found to have CBD stones. The three patients in whom no ERC was performed despite an appropriate indication represent a failure to adhere to the protocol described.

Discussion

There now seems to be little doubt that laparoscopic cholecystectomy is the procedure of choice for patients with symptomatic gallbladder stones[1,5,6]. However, management of the patient with CBD stones is far more controversial. The adoption of a management protocol that minimizes the need for open operation aims to decrease the morbidity and mortality associated with the traditional open approach.

In treating a benign disease it must first be ensured that any new policy adopted does not incur a higher mortality rate. A few avoidable deaths will counter any benefit accrued from the application of minimally invasive techniques. In patients aged <60 years the mortality rate associated with open duct exploration is about 1 per cent, but in patients older than this the mortality rate rises steeply[7,8]. The mortality rate of ERC, sphincterotomy and duct clearance is around 1 per cent[9,10]. ERC and sphincterotomy has gained acceptance in the management of retained stones after operation or in the high-risk patient in whom one would wish to avoid surgery. The controversy surrounds the use of preoperative ERC in otherwise fit patients with the gallbladder *in situ*. On balance, taking all the available literature into consideration, there is no evidence that the use of ES increases mortality in the management of symptomatic CBD stones[10–13]. This view is supported by the present findings, which show that the adoption of a minimally invasive approach to the management of CBD calculi based on ES is safe, with no deaths in patients aged <70 years and an overall mortality rate of only 2 per cent.

The use of ES, particularly in the younger patient, is not without problems[14]. There is a theoretical but unproven risk of late distant complications in the liver, pancreas, stomach or colon as a result of alterations in bile salt turnover. When this protocol was devised there was no alternative to ES for the treatment of patients with choledocholithiasis by minimally invasive techniques. However, during the study period it became possible to explore the CBD laparoscopically[15]. In the seven patients in whom this was attempted the duct was cleared in six. The only failure was due to equipment breakdown and not a failure of the technique itself. While at present this procedure is fairly time consuming (median 200 min) it does not appear to affect adversely the recovery from surgery. The median stay after laparoscopic duct exploration was 2 days in the present study. We expect that operative time will fall with further technical advances and experience.

The optimum method for clearing the duct laparoscopically has yet to be determined, but a combination of the techniques described here has enabled the successful treatment of small, large and multiple duct stones. The curved introducer is considered a significant advance because it both reduces the risk of damage to the choledochoscope and facilitates exploration of both the proximal and distal biliary tree. Technical advances such as 'picture-in-picture' video equipment to enable the simultaneous display of both laparoscopic and choledochoscopic images will also enable more widespread use of this technique. It is envisaged that laparoscopic CBD exploration will become the treatment of choice for common duct stones, particularly in patients aged <50 years, with preoperative ES being reserved for the elderly high-risk patient.

The management of patients whose primary problem is symptomatic gallbladder stones is more contentious now that laparoscopic cholecystectomy is widely practised. The present policy of preoperative ERC in patients with a history of obstructive jaundice, dilated CBD or raised liver enzyme levels resulted in just one patient (0·6 per cent) being found to have unexpected CBD stones on operative cholangiography. Others have found that a selective policy has been associated with a similar incidence of unexpected duct calculi and has also reduced overall costs of treatment[16,17]. Although it was not possible to perform cholangiography in all patients at laparoscopic cholecystectomy for technical reasons, no patient who did not have ERC before operation or intraoperative cholangiography has subsequently presented clinically with a common duct stone. Indeed, the inability to perform operative cholangiography because of a small cystic duct seems to be associated with a very low incidence of CBD stones. Others have advocated the routine use of preoperative cholangiography[18]. Although this examination is a sensitive way of detecting common duct stones[19], it does not enable the calculi to be dealt with before laparoscopic cholecystectomy. Indeed, if laparoscopic duct exploration were to become more widely available then the use of preoperative intravenous cholangiography could conceivably be less useful.

In conclusion, this study has shown, first, that more than 95 per cent of patients with CBD stones can be managed successfully using minimally invasive techniques and, second, that the selective use of preoperative ERC and intraoperative cholangiography enables the safe use of laparoscopic cholecystectomy in all patients, with a low probability of missed CBD stones. Finally, and of more interest, is the finding that laparoscopic duct exploration can be performed successfully in the majority of patients in whom it is required. Open duct exploration is therefore likely to become a much less frequently performed procedure.

References

1. Martin IG, Holdsworth PJ, Asker J *et al.* Laparoscopic cholecystectomy as a routine procedure for gallstones: results of an 'all-comers' policy. *Br J Surg* 1992; **79**: 807–10.
2. Scott-Coombes D, Thompson J. Bile duct stones and laparoscopic cholecystectomy. *BMJ* 1991; **303**: 1281–2.
3. Polydorou AA, Dowsett JF, Vaira D *et al.* Needle knife sphincterotomy – an initial experience. *Gut* 1988; **29**: A1490.
4. Hunter JG. Laparoscopic transcystic duct exploration. *Am J Surg* 1992; **163**: 53–8.
5. Southern Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. *N Engl J Med* 1991; **324**: 1073–8.
6. Cuschieri A, Dubois F, Mouiel J *et al.* The European experience with laparoscopic cholecystectomy. *Am J Surg* 1991; **161**: 385–7.
7. McSherry CK. Cholecystectomy: the gold standard. *Am J Surg* 1989; **158**: 174–8.
8. Meyer KA, Capos NJ, Mittelpunkt AI. Personal experience with 1261 cases of acute and chronic cholecystitis and cholelithiasis. *Surgery* 1967; **61**: 661–8.
9. Cotton PB. Endoscopic management of bile duct stones; (apples and oranges). *Gut* 1984; **25**: 587–97.
10. Heinerman PM, Boeckl O, Pimpl W. Selective ERCP and preoperative stone removal in bile duct surgery. *Ann Surg* 1989; **209**: 267–72.
11. Neoptolemos JP, Shaw DE, Carr-Locke DL. A multivariate analysis of preoperative risk factors in patients with common bile duct stones: implications for treatment. *Ann Surg* 1989; **209**: 157–61.
12. Neoptolemos JP, Carr-Locke DL, Fossard DP. Prospective randomized study of preoperative endoscopic surgery *versus* surgery alone for common bile duct stones. *BMJ* 1987; **294**: 470–4.

13. Miller BM, Kozarek RA, Ryan JA, Ball TJ, Traverso LW. Surgical *vs* endoscopic management of common bile duct stones. *Ann Surg* 1988; **207**: 135–41.
14. Vallon AG, Holton JM, Cotton PB. Clinical and endoscopic follow up after endoscopic sphincterotomy. *Gut* 1982; **22**: A889.
15. Petelin JB. Laparoscopic approach to common duct pathology. *Surg Laparosc Endosc* 1991; **1**: 33–41.
16. Pernthaler H, Sandbichler P, Schmid T, Margreiter R. Operative cholangiography in elective cholecystectomy. *Br J Surg* 1990; **77**: 399–400.
17. Taylor TV, Torrance B, Rimmer S, Hillier V, Lucas SB. Operative cholangiography: is there a statistical alternative? *Am J Surg* 1983; **145**: 640–3.
18. Joyce WP, Keane R, Burke GJ *et al.* Identification of bile duct stones in patients undergoing laparoscopic cholecystectomy. *Br J Surg* 1991; **78**: 1174–6.
19. Huddy SPJ, Southam JA. Is intravenous cholangiography an alternative to the routine peroperative cholangiogram? *Postgrad Med J* 1989; **65**: 896–9.

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Plasminogen activator inhibitor 2 reduces peritoneal fibrinolytic activity in inflammation

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Fibrinolysis in peritoneal tissue may play a role in the development of intra-abdominal adhesions. The plasminogen-activating capacity of human peritoneum results largely from the presence of tissue plasminogen activator (tPA). Inflammation reduces peritoneal plasminogen-activating activity and leads to the appearance of plasminogen activator inhibitor (PAI) type 1. The role of PAI-2 in the inhibition of peritoneal fibrinolysis during inflammation was investigated in this study. The plasminogen-activating activity of peritoneal biopsy homogenates (seven inflamed, seven normal), measured using a fibrin plate technique, was reduced in inflamed compared with normal tissue (median <0·07 versus *13·9 units/cm*^{2}, $P<0{\cdot}01$)*; tPA antigen levels were not significantly different (median 1·02* versus *1·34 ng/ml). PAI-1 and PAI-2 antigens were not detected in normal human peritoneum but were present in inflamed peritoneum (median concentration 8·8 ng/ml for PAI-1, 26·7 ng/ml for PAI-2). These inhibitors may be important factors in adhesion formation by contributing to the abolition of peritoneal plasminogen-activating activity.*

Human and animal peritoneum possess fibrinolytic activity[1,2], which is reduced following physical, chemical and ischaemic trauma[3–5]. Fibrinous adhesions occur after such insults and the level of fibrinolytic activity may determine whether fibrin deposits are lysed, leading to resolution, or become organized into permanent fibrous adhesions[6,7]. Tissue plasminogen activator (tPA) is the principal plasminogen activator in human peritoneum, and plasminogen activator inhibitor (PAI) type 1 may be responsible for the reduction in plasminogen-activating activity seen in inflammation[8].

PAI-2 is another member of the serine protease inhibitors (serpins)[9,10]. PAI-2 differs from PAI-1 in its immunological reactivity, molecular weight, cellular origin and reaction rate with tPA. This study investigated the role of PAI-2 in the inhibition of peritoneal plasminogen-activating activity in inflammation.

Patients and methods

Patients

Paired peritoneal biopsies were taken from seven patients undergoing elective abdominal surgery (normal controls) and from seven undergoing emergency surgery for appendicitis ($n = 5$) or perforated viscus ($n = 2$). Patients gave informed consent and the study was approved by the local hospital ethical committee.

Biopsy technique

Parietal peritoneum was biopsied as soon as possible after opening the abdominal cavity, using disposable 6-mm diameter biopsy punches (Stiefel Laboratories, Wooburn Green, UK). The disc of peritoneum was dissected off the underlying tissue, wrapped in foil and snap-frozen in liquid nitrogen before transfer to a freezer at −80°C.

Preparation of peritoneal homogenate

Peritoneal biopsy homogenates were prepared as previously described[5]. Briefly, biopsies were thawed rapidly at room temperature, weighed, rinsed in buffer and homogenized in buffer containing detergent (Triton X100; Sigma Chemicals, Poole, UK). The homogenate was centrifuged at 12 000g for 20 min and aliquots of the supernatant stored at −20°C for no longer than 4 weeks before assay.

Plasminogen-activating activity assay

The plasminogen-activating activity of peritoneal homogenates was determined using a standard fibrin plate assay[11]. A solution of fibrinogen, plasminogen and buffer was clotted in the base of a Petri dish using bovine thrombin. Aliquots of 20 μl of peritoneal homogenates and standard dilutions of tPA (2nd International Standard; National Institute for Biological Standards and Controls, Mill Hill, UK) were placed in central wells cut in these fibrin layers. After overnight incubation at 37°C the zone of lysis around the central well was measured and the results expressed in units of tPA per square centimetre of peritoneum. The lower limit of sensitivity of the assay was 0·07 units/cm^2. Plate lysis was abolished by prior heating at 80°C for 20 min, confirming that fibrinolysis was plasminogen mediated.

Immunoassays

The peritoneal homogenates were analysed for antigenic levels of tPA, PAI-1 and PAI-2 using enzyme-linked immunosorbent assays (Porton Cambridge, Maidenhead, UK). The lower limits of detection for these assays were 0·75, 2·5 and 6·0 ng/ml respectively. Standard solutions of PAI-1 did not cross-react with the antibodies present in the PAI-2 kit or vice versa.

Statistical analysis

The Mann–Whitney U test and Spearman rank correlation coefficient (r_S) were used.

Results

Median (range) plasminogen-activating activity was significantly reduced in inflamed peritoneum compared with normal tissue (<0·07 (<0·07–0·42) *versus* 13·9 (8·3–22·9) units/cm^2, $P<0{\cdot}01$). There was no significant difference in median (range) levels of tPA (1·02 (<0·75–1·82) *versus* 1·34 (<0·75–1·50) ng/ml respectively). Neither PAI-1 nor PAI-2 was detected in normal peritoneum but both were present in samples from inflamed peritoneum (PAI-1 <2·5 *versus* 8·8 (range 2·7–21·0) ng/ml, $P<0{\cdot}01$; PAI-2 <6·0 *versus* 26·7 (range 10·3–106·5) ng/ml, $P<0{\cdot}01$) (*Figure 1*). The levels of the two inhibitors showed a positive correlation in samples of inflamed tissue ($r_S = 0{\cdot}96$, $P<0{\cdot}001$) (*Figure 2*).

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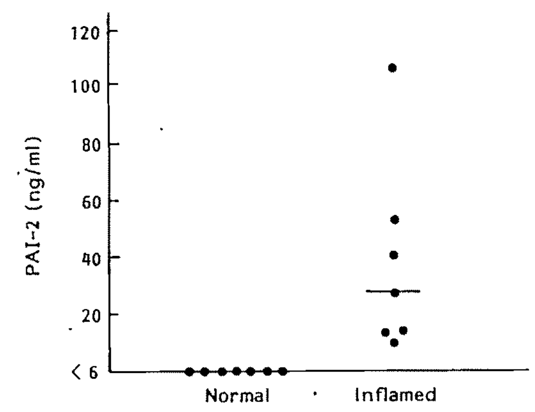

Figure 1 *Plasminogen activator inhibitor 2 (PAI-2) content of normal and inflamed peritoneal biopsy homogenates. Bars are medians*

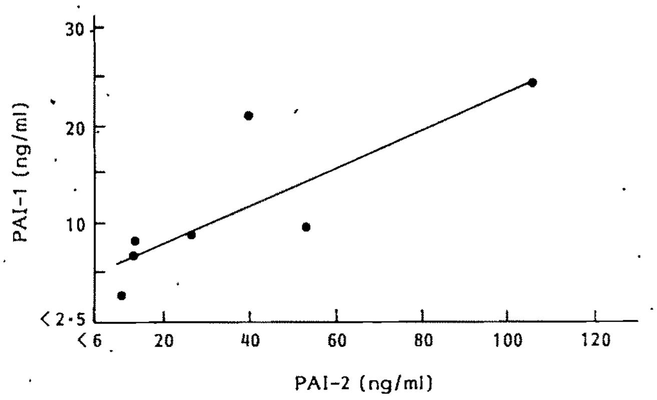

Figure 2 *Correlation between plasminogen activator inhibitor (PAI) 1 and 2 in inflamed peritoneal biopsy homogenates* (n = 7). $r_S = 0{\cdot}96$, $P < 0{\cdot}001$

Discussion

Functional fibrinolytic activity of peritoneum is affected by the levels of tPA, previously shown to be the major activator in peritoneum, and PAIs. Peritoneal plasminogen-activating activity is reduced in inflammation[8] and this is secondary to an increase in levels of PAI-1. The present study suggests that PAI-2 may also make a contribution to the reduced plasminogen-activating activity seen in inflammation.

PAI-2 was first purified from placental tissue[12]. It has since been isolated from the plasma of pregnant women[13] and from a number of different cell lines such as monocyte/macrophages[14,15], fibroblasts[16], and lymphoma[17] and leukaemic[18] cells. An inhibitor of fibrinolysis had been previously isolated from bovine peritoneal mesothelium but its identity was not known[19].

The levels of PAI-1 and PAI-2 in cell lines, including cultured human omental mesothelial cells, can be increased by the presence of bacterial lipopolysaccharide and inflammatory mediators such as interleukin 1 and tumour necrosis factor[20–24]. Such molecules are probably present in the peritoneum following inflammation and may explain the presence of PAI-2 demonstrated *in vivo*. PAI-1 and PAI-2 would inhibit lysis of fibrinous deposits within the abdominal cavity and therefore promote adhesion formation. PAI-2 is a less efficient[10] inhibitor of tPA than PAI-1 and may function as a reserve inhibitor of fibrinolysis within the peritoneal cavity.

The levels of both PAI-1 and PAI-2 were raised in inflamed peritoneum, but their production is thought to be independently regulated, at least in human umbilical cord vein endothelial cells[25].

This study provides further understanding of the mechanism controlling fibrinolysis in the peritoneal cavity. The use of antagonists of PAIs may lead to the development of specific methods of adhesion prophylaxis and treatment.

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References

1. Porter JM, McGregor FH, Mullen DC, Silver D. Fibrinolytic activity of mesothelial surfaces. *Surgical Forum* 1969; **20**: 81–2.
2. Myhre-Jensen O, Larsen SB, Astrup T. Fibrinolytic activity in serosal and synovial membranes. *Arch Pathol* 1969; **88**: 623–30.
3. Gervin AS, Puckett CL, Silver D. Serosal hypofibrinolysis. A cause of postoperative adhesions. *Am J Surg* 1973; **125**: 80–7.
4. Buckman RF, Woods M, Sargent L, Gervin AS. A unifying pathogenetic mechanism in the etiology of intraperitoneal adhesions. *J Surg Res* 1976; **20**: 1–5.
5. Thompson JN, Paterson-Brown S, Harbourne T, Whawell SA, Kalodiki E, Dudley HAF. Reduced human peritoneal plasminogen activating activity: possible mechanism of adhesion formation. *Br J Surg* 1989; **76**: 382–4.
6. Buckman RF, Buckman D, Hufnagel HV, Gervin AS. A physiologic basis for the adhesion free healing of deperitonealized surfaces. *J Surg Res* 1976; **21**: 67–76.
7. Raftery AT. The effect of peritoneal trauma on peritoneal fibrinolytic activity and intraperitoneal adhesion formation. *Eur Surg Res* 1981; **13**: 397–401.
8. Vipond MN, Whawell SA, Thompson JN, Dudley HAF. Peritoneal fibrinolytic activity and intra-abdominal adhesion formation. *Lancet* 1990; **335**: 1120–2.
9. Sprengers ED, Kluft C. Plasminogen activator inhibitors. *Blood* 1987; **69**: 381–7.
10. Kruithof EKO. Inhibitors of plasminogen activators. In: Kluft C, ed. *Tissue Type Plasminogen Activator: Physiological and Clinical Aspects*. Boca Raton, Florida: CRC Press, 1988: 189–210.
11. Astrup T, Mullertz S. The fibrin plate method for estimating fibrinolytic activity. *Arch Biochem Biophys* 1952; **40**: 346–51.
12. Astedt B, Lecander I, Brodin T, Lunblad A, Low K. Purification of a specific placental plasminogen activator inhibitor by monoclonal antibody and its complex formation with plasminogen activator. *Thromb Haemost* 1985; **53**: 122–5.
13. Lecander I, Astedt B. Isolation of a new specific plasminogen activator inhibitor from pregnancy plasma. *Br J Haematol* 1986; **62**: 221–8.
14. Chapman HA, Vavrin Z, Hibbs JB. Macrophage fibrinolytic activity: identification of two pathways of plasmin formation by intact cells and of a plasminogen activator inhibitor. *Cell* 1982; **28**: 653–62.
15. Saksela O, Hovi T, Vaheri A. Urokinase-type plasminogen activator and its inhibitor secreted by cultured human monocyte-macrophages. *J Cell Physiol* 1985; **122**: 125–32.
16. Michel JB, Quertermous T. Modulation of mRNA levels for urinary and tissue type plasminogen activator and plasminogen activator inhibitors 1 and 2 in human fibroblasts by interleukin 1. *J Immunol* 1989; **143**: 890–5.
17. Kruithof EKO, Vassalli J-D, Schleuning W-D, Mattalianno RJ, Bachmann F. Purification and characterisation of a plasminogen activator inhibitor from the histiocytic lymphoma cell line U-937. *J Biol Chem* 1986; **261**: 11207–13.
18. Takeuchi T, Niiya K, Kubonishi I, Miyoshi I. A plasminogen activator inhibitor-2 from a promyelocytic leukemic cell line, PL-21, binds to the carboxy-terminal chain of plasminogen activators. *Thromb Haemost* 1990; **63**: 259–64.
19. Pugath EMJ, Poole JCF. Inhibitor of fibrinolysis from mesothelium. *Nature* 1969; **221**: 269–70.
20. Bevilacqua MP, Schleef RR, Gimbrine MA, Loskutoff DJ. Regulation of the fibrinolytic system of cultured human vascular endothelium by interleukin 1. *J Clin Invest* 1986; **78**: 587–91.
21. Emeis JJ, Kooistra T. Interleukin 1 and lipopolysaccharide induce an inhibitor of tissue type plasminogen activator *in vivo* and in cultured endothelial cells. *J Exp Med* 1986; **163**: 1260–6.
22. Hanss M, Collen D. Secretion of tissue type plasminogen activator and plasminogen activator inhibitor by cultured human endothelial cells: modulation by thrombin, endotoxin and histamine. *J Lab Clin Med* 1987; **109**: 97–107.
23. Van Hinsberg VWM, Kooistra T, Van den Berg EA, Princen HMG, Fiers W, Emeiss JJ. Tumour necrosis factor increases the production of plasminogen activator inhibitor in

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24. Van Hinsberg VWM, Kooistra T, Scheffer MA, Van Bockel JH, Van Muijen GNP. Characterisation and fibrinolytic properties of human omentum tissue mesothelial cells. Comparison with endothelial cells. *Blood* 1990; **75**: 1490–7.
25. Schleef RR, Wagner NV, Loskutoff DJ. Detection of both type 1 and type 2 plasminogen activator inhibitors in human cells. *J Cell Physiol* 1988; **134**: 269–74.

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Surgical workshop

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Laparoscopically assisted reversal of Hartmann's procedure

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The disadvantage of Hartmann's procedure in the management of diverticular disease is that reversal is a major undertaking associated with significant morbidity and mortality. A number of patients refuse or are never considered fit and up to 60 per cent do not undergo reversal[1]. A minimally invasive technique for reversal might offer advantages.

Surgical technique

A 60-year-old woman weighing 89 kg was admitted with generalized peritonitis. Laparotomy showed a perforated sigmoid diverticulum with purulent peritonitis. The left colon was mobilized proximal to the splenic flexure and 16 cm of colon, including the diverticular mass, was excised. The rectum was staple-transected at the peritoneal reflection and a left iliac fossa end colostomy constructed. The patient returned 4 months later for restoration of colonic continuity.

Reversal was carried out laparoscopically with the patient in the Lloyd-Davies position. The colostomy was mobilized through a 6-cm elliptical incision and after entry into the peritoneal cavity the descending colon was freed by sharp dissection until it could be delivered 10 cm from the abdominal wall. The distal 3 cm was resected and the head of a CDH29 circular stapling device (Ethicon, Edinburgh, UK) inserted. Adhesions to the anterior abdominal wall were mobilized under direct vision and two 10/11-mm Endopath cannulas (Ethicon) inserted under direct vision above and below the colostomy incision, after which the exteriorized colon with the CDH head was returned to the peritoneal cavity and the incision closed. Pneumoperitoneum was induced through one of these cannulas, obviating the need for blind insertion of Veress needle and trocar–cannula, a concern in reoperative surgery. The telescope was introduced through the upper cannula and adhesiolysis started. A third 10/11-mm port was established at the level of the colostomy in a 'mirror image' site on the right side. The uterus was retracted anteriorly using Endopath Allis graspers and the ureters identified in the retroperitoneum, which was not opened. The small bowel was mobilized out of the pelvis using the Endopath-Babcock, exposing the pouch of Douglas. The CDH29 was inserted anally to identify and project the rectal stump and the axle of the stapler head advanced through the apex of the rectal stump under direct vision. Through a fourth suprapubic 10/11-mm cannula the head of the stapler was approximated with the Babcock and anastomosis performed without tension and with two complete 'doughnuts'. Integrity of the anastomosis was checked by rectal instillation of dye. The operating time was 95 min; no drain was used. The patient was discharged on day 5 and has had no late complications.

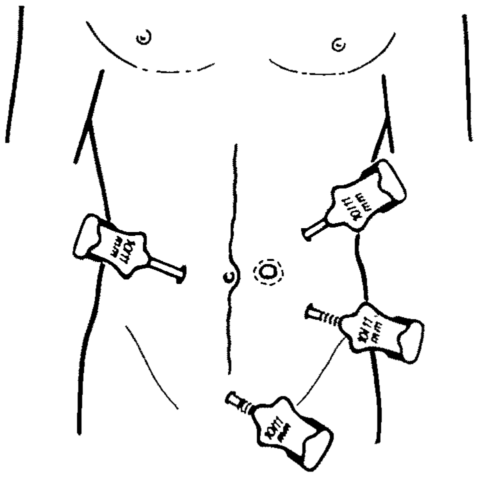

Figure 1 *Port positions for the laparoscopic procedure*

Discussion

In some patients, laparoscopic mobilization of the left colon and splenic flexure may be necessary but this had been carried out at the primary operation in the patient discussed. The whole operation, apart from colostomy mobilization, would be feasible laparoscopically but, with anticipation, mobilization of the left colon at the first operation facilitates reanastomosis. In a 5-year audit of Hartmann's procedure for cancer[2], the median hospital stay of those undergoing reanastomosis successfully was 17 (range 8–48) days. The laparoscopic procedure may lead to shorter hospital stay and increased patient acceptance. The technique may have limited application because of dense inflammatory adhesions in the pelvis and, as with other laparoscopic procedures, the surgeon must be prepared to convert to laparotomy if required.

References

1. Liebert CW, De Weese BM. Primary resection without anastomosis for perforation of acute diverticulitis. *Surg Gynecol Obstet* 1981; **152**: 30–2.
2. Dixon AR, Holmes JT. Hartmann's procedure for carcinoma of rectum and distal sigmoid colon: 5 year audit. *J R Coll Surg Edinb* 1990; **35**: 166–8.

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Controlled trial of wound infiltration with bupivacaine for postoperative pain relief after appendicectomy in children

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A double-blind controlled trial was performed to assess the effectiveness of wound infiltration with bupivacaine for postoperative pain relief after appendicectomy in children. Sixty children entered the trial and 52 completed it; they were randomized to receive bupivacaine or placebo. Assessment of postoperative pain using a numerical scoring system was made by the child, the recovery sister and the ward sister, and by measurement of the time between the end of the operation and the need for narcotic injection. Analysis revealed significantly less pain ($P < 0\cdot03$) *in the immediate postoperative period in the treated group. The use of bupivacaine wound infiltration as a supplement to other current methods of pain control is recommended.*

Postoperative pain control using local or regional anaesthesia to supplement general anaesthesia is a topic of current interest. Wound infiltration, nerve blockade and caudal anaesthesia have been used successfully in paediatric surgical operations and are particularly well established in inguinal procedures[1–3].

In appendicectomy, one of the most common operations in children and adults, intercostal blockade has been used[4] but, although the standard muscle-splitting incision lends itself to wound infiltration, this technique has been little used. This study reports a controlled trial designed to assess the efficacy of wound infiltration after appendicectomy in children.

Patients and methods

The protocol was approved by the Hunter Area Research Ethics Committee and all parents gave informed consent.

The patients were children 5–14 years of age under the care of the author who underwent appendicectomy with the clinical diagnosis of uncomplicated acute appendicitis. The upper age limit was dictated by the author's paediatric surgical practice and the lower limit by the degree of cooperation that could be expected of a child in the assessment of postoperative pain.

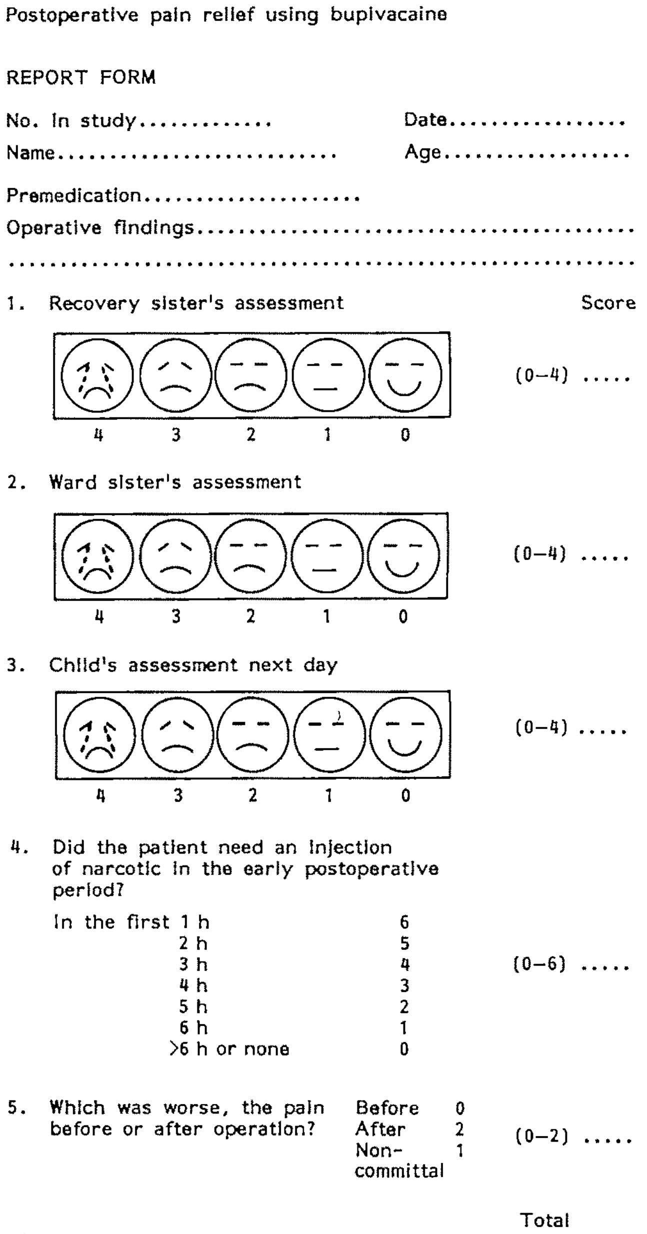
The following patients with appendicitis were excluded from the trial: those whose parents refused consent (only one did so); those with clinical or operative evidence of complicated appendicitis such as perforation, peritonitis or abscess; and those in whom the protocol was inadvertently breached.

A standard premedication (Omnopon-Scopolamine – papaveretum 320 μg/kg and hyoscine hydrobromide 6·4 μg/kg; David Bull Laboratories, Mulgrave, Victoria, Australia) was given by intramuscular injection 1 h before operation. Anaesthetic technique was standardized and intraoperative narcotic agents avoided. All patients received preoperative and peroperative antibiotics, usually cefoxitin. Operations were performed by the author or a senior registrar, using a consistent technique involving a skin crease incision and a McBurney gridiron muscle-splitting approach.

Identical numerically identified randomized ampoules of bupivacaine 0·25 per cent or normal saline were used consecutively. After closure of the peritoneum, the trial fluid was injected into the plane between the internal oblique and transversus muscles, upwards and laterally to achieve blockade of the intercostal nerves supplying the wound. The muscular belly of the external oblique and the subcutaneous tissues were infiltrated, using a total dose of the trial fluid of 0·5 ml/kg. Aspiration was performed before each injection to avoid intravenous injection of bupivacaine.

In the postoperative period, pain relief was afforded by intermittent intramuscular narcotic injections. The recovery and ward nursing staff used their ordinary clinical judgement to decide on administration of analgesia.

Postoperative pain was measured by several methods and was



Postoperative pain relief using bupivacaine

REPORT FORM

No. in study............. Date.................
Name........................... Age..................

Premedication.....................
Operative findings...
....

1. Recovery sister's assessment — Score

4 3 2 1 0 — (0–4) .....

2. Ward sister's assessment

4 3 2 1 0 — (0–4) .....

3. Child's assessment next day

4 3 2 1 0 — (0–4) .....

4. Did the patient need an injection of narcotic in the early postoperative period?

In the first 1 h	6	
2 h	5	
3 h	4	(0–6) .....
4 h	3	
5 h	2	
6 h	1	
>6 h or none	0	

5. Which was worse, the pain before or after operation?

Before	0	
After	2	(0–2) .....
Non-committal	1	

Total ______

Figure 1 *Report form*

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recorded on a score sheet (*Figure 1*). Visual analogue scales as described by Maunuksela and colleagues[5] constituted the first method (parameters 1–3, *Figure 1*). The recovery sister assessed the child after waking from anaesthesia and gave a score of 0–4 according to assessment of the pain (parameter 1, *Figure 1*). The child stayed in recovery for 1·5 h. On return to the children's ward, the ward sister gave a further assessment using the same method (parameter 2, *Figure 1*). Next day, when fully recovered, the child gave his or her own assessment of the pain experienced on waking from anaesthesia, again using the visual analogue method (parameter 3, *Figure 1*).

The second method was based on the interval between the end of the operation and the first narcotic injection, if any (parameter 4, *Figure 1*). The score (0–6), not the actual time, was used.

The third method of pain measurement was self-assessment by the child when asked next day to compare the severity of preoperative and postoperative pain, using a score of 0–2 (parameter 5, *Figure 1*).

The sum of scores for parameters 1–5 was also taken, this total being $\leqslant 20$.

Results were analysed using an IBM computer with the Minitab statistical package (Minitab V 7.1; Minitab, Pennsylvania, USA).

Results

Sixty patients entered the trial. Eight were excluded because of breach of protocol (premedication not given, narcotic used during anaesthesia, peritonitis found at operation). Twenty-four received bupivacaine, 28 saline (*Table 1*). There were 32 boys and 20 girls.

Forty-four (85 per cent) of the patients had histologically proven appendicitis, 22 in each group. Only one child had a superficial wound infection; this patient received saline (*Table 1*).

Table 2 shows the mean scores for each parameter assessed. There was no difference between pain scores reported by boys and girls, and all children tended to record a middle value (usually 2) for parameter 3. The total score was significantly lower ($P = 0{\cdot}028$) in the bupivacaine-treated group. The time interval between operation and narcotic injection was also considerably longer in the bupivacaine-treated children ($P = 0{\cdot}015$). The total number of injections needed in the whole of the postoperative period was the same in treated and control groups (mean 1·9).

Table 1 *Comparison of treated and control groups*

	Bupivacaine ($n = 24$)	Saline ($n = 28$)
Sex ratio (M:F)	17:7	15:13
Mean age (years)	10·3	9·4
Acute appendicitis	22	22
Other pathology	1	1
Normal appendix	1	5
Wound infection	0	1

There were no statistically significant differences between the groups

Table 2 *Pain scores recorded for each item on the report form* (Figure 1)

Pain score parameter	Bupivacaine ($n = 24$)	Saline ($n = 28$)
1	0·8	1·4
2	1·1	1·6
3	1·8	2·1
4	0·8	2·2
5	0·5	0·5
Total	5·0(3·7)*	7·7(4·7)

Values are mean(s.d.). $*P = 0{\cdot}028$ (two-sample t test)

Discussion

It has been shown that the injection of the long-acting local anaesthetic bupivacaine after appendicectomy in children affords pain relief in the early postoperative period and delays the need for narcotic injection. This technique is not an alternative to narcotic injection but a valuable adjunct that allows the patient to wake more comfortably. It is simple to administer and safe, provided due attention is given to dosage and to avoiding intravenous injection. It does not predispose to wound infection.

Bupivacaine infiltration of the wound is a worthwhile supplement to current methods of postoperative pain relief. Even if it only delays the need for postoperative analgesia, it helps the child through the critical recovery period by easing the pain experienced on waking from the anaesthetic. If patient-controlled analgesia is to be used, peroperative local anaesthesia allows the patient to recover sufficiently to use the device effectively.

At the present time, bupivacaine is the longest acting local anaesthetic available. Loder[6] reported that its duration of action was prolonged by the addition of dextran, although Armstrong and Kingsnorth[7] did not confirm this. Tverskoy *et al.*[8] studied postoperative pain after herniorrhaphy in adults and showed that the use of local or spinal bupivacaine combined with general anaesthesia afforded pain relief for a prolonged period well beyond the duration of its pharmacological action. They postulated that the local anaesthetic 'suppresses the formation of the sustained hyperexcitable state in the central nervous system that is responsible for maintenance of postoperative pain'.

The present study demonstrates a clear reduction in pain score and delay for analgesic requirement in children who received infiltration of the wound with bupivacaine after appendicectomy.

Acknowledgements

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References

1. McGrath PJ, Unruh AM. *Pain in Children and Adolescents.* Amsterdam: Elsevier, 1987.
2. Langer JC, Shandling B, Rosenberg M. Intraoperative bupivacaine during outpatient hernia repair in children: a randomized double blind trial. *J Pediatr Surg* 1987; **22**: 267–70.
3. Lafferty PM, Gordon NH, Winning TJ. A comparison of post-operative pain relief techniques in orchidopexy. *Ann R Coll Surg Engl* 1990; **72**: 7–8.
4. Bunting P, McGeachie JR. Intercostal nerve blockade producing analgesia after appendicectomy. *Br J Anaesth* 1988; **61**: 169–72.
5. Maunuksela EL, Olkkola KT, Korpela R. Measurement of pain in children with self-reporting and behavioural assessment. *Clin Pharmacol Ther* 1987; **42**: 137–41.
6. Loder RE. A local anaesthetic solution with longer action. *Lancet* 1960; **ii**: 346–7.
7. Armstrong DN, Kingsnorth AN. Local anaesthesia in inguinal herniorrhaphy: influence of dextran and saline solution on duration of action of bupivacaine. *Ann R Coll Surg Engl* 1986; **68**: 207–8.
8. Tverskoy M, Coxacov L, Ayache M, Bradley EL Jr, Kissin I. Postoperative pain after inguinal herniorrhaphy with different types of anesthesia. *Anesth Analg* 1990; **70**: 29–35.

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Ischaemia–reperfusion injury in the rat kidney: effect of a single dose of sodium bicarbonate

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The protective effect of intravenous 8·4 per cent sodium bicarbonate on renal function after ischaemia was evaluated in rats subjected to 45 or 90 min warm unilateral renal ischaemia. Two groups of control animals received normal or 3 per cent saline. All solutions were given by bolus injection 3 h before ischaemia. Renal function was significantly protected in animals receiving bicarbonate. Vascular congestion of the inner stripe of the renal medulla was prevented. The survival rate in the group undergoing 90-min ischaemia was 70 per cent for animals receiving bicarbonate and nil in those given saline. Preoperative alkalinization confers significant functional and morphological protection in the ischaemic kidney.

The pathogenesis of postischaemic renal injury remains unclear. Anoxia may play an initiating role but tubular cell swelling, tubular obstruction, venous outflow obstruction and reduced cortical blood flow have all been implicated in the process[1–4]. Other experiments[5–10] have shown that a medullary perfusion defect develops after reperfusion, and oxygen free radicals may be causative and play a role in the pathogenesis of postischaemic renal failure. Saline, mannitol, inosine, frusemide, allopurinol, superoxide dismutase and verapamil have all been used experimentally or clinically with varying degrees of success to modulate this injury[9–14].

Fitzpatrick *et al.*[15] demonstrated that oral administration of 2 per cent sodium bicarbonate for 2 weeks before ischaemia provided effective postischaemic functional protection. Atkins[16] showed the same protection using oral bicarbonate for 3 days before experimental ischaemia. Acute intravenous bicarbonate loading has been used prophylactically and therapeutically for acute renal failure in the clinical setting[17–19]. There are, however, few experimental data on the effects of intravenous sodium bicarbonate as a single dose immediately before renal ischaemia.

The aims of this study were: to determine the protective effect of intravenous 8·4 per cent sodium bicarbonate administered immediately before experimental renal ischaemia; to define the timing of injections required for protection to occur; to assess the effects of this treatment on medullary vascular perfusion and systemic and urinary acid–base balance; and to exclude a direct effect of sodium loading *per se* by inclusion of a control group treated with 3 per cent saline.

Materials and methods

Under halothane anaesthesia, acute unilateral renal ischaemia was induced in six groups of ten male Wistar rats. The animals were aged 3–4 months and weighed (mean(s.d.)) 250(50) g. Groups 1–3 underwent ischaemia for 45 min and groups 4–6 for 90 min. At 3 h before ischaemia, animals were given 1 ml 8·4 per cent sodium bicarbonate intravenously (groups 1 and 4), 1 ml normal saline (groups 2 and 5) or 2 ml 3 per cent saline (groups 3 and 6). The decision to give treatment at 3 h before ischaemia was based on a pilot study that showed inadequate protection if given at 1 or 2 h. Solutions were administered via the sublingual vein using a brief halothane anaesthetic. At the end of the ischaemia period, contralateral nephrectomy was performed.

Serum creatinine levels were measured before operation and 1, 3 and 7 days after ischaemia. The rats were killed on day 7 and the kidneys removed and examined histologically. If death occurred before day 7, the date and time were noted and the kidney harvested for histological examination. In a separate group of five bicarbonate-treated rats subjected to 90-min ischaemia, the kidneys were harvested on day 4.

Histological sections were examined at low and high power after staining with Marsh's scarlet blue stain. A vascular congestion index (VCI) was generated for each of the four vascular regions of the kidney (cortex, outer and inner stripes of medulla, inner medulla) by adding the total number of congested blood vessels per low-power field (10 × magnification) seen in ten low-power fields in each vascular region. This procedure was automated using the Kontron Mopp Videoplan Image Analyser (Kontron Electronics, Munich, Germany).

In the second limb of the experiment, the effects of the pretreatments on blood and urinary acid–base balance and 24-h urinary sodium excretion were assessed. Four groups of five male Wistar rats were placed in metabolic cages for 24 h and allowed free access to food and water. Urine was collected for 24 h for pH measurement and baseline sodium excretion determination. After treatment with sodium bicarbonate, normal saline or 3 per cent saline, pH and baseline sodium excretion were measured again. The control group received no treatment. At 3 h after treatment 2 ml carotid blood was obtained for acid–base studies.

Serum creatinine values for each group are given as mean(s.e.m.). Statistical comparisons between control and bicarbonate-treated animals were made using one-way analysis of variance, followed by tests between individual means by Fisher's least significant differences criterion if the overall F value was significant. The data on the VCI and urine acid–base studies were analysed similarly.

Results

All rats in groups 1–3 survived 7 days after operation, demonstrating that 45-min ischaemia was a sublethal insult. The extent of renal functional damage as assessed by day 3 peak serum creatinine levels was, however, significantly less ($P < 0\cdot001$) in the sodium bicarbonate-treated animals (*Figure 1*). Rats in group 4 (pretreated with sodium bicarbonate) showed significant protection against 90-min renal ischaemia compared with controls and saline-pretreated animals ($P < 0\cdot001$) (*Figure 2*).

The 7-day survival rate in group 4 was 70 per cent, three rats dying on the fourth day after operation. All animals in groups 5 and 6 died on the fourth day after operation. Median survival times for group 5 and 6 animals were 80 and 79 h respectively, compared with 82 h for the three group 4 animals. The remaining seven rats in group 4 were killed as planned.

Blood pH and bicarbonate levels 3 h after bicarbonate administration demonstrated a systemic alkalosis compared with the normal and 3 per cent saline controls. This was reflected in the pH of the urine in the first 24 h after treatment (*Table 1*). There was no significant difference in 24-h urinary sodium excretion between sodium bicarbonate- and 3 per cent saline-treated animals.

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There were no macroscopic differences in the appearance of bivalved kidneys from groups 1, 2 or 3. Histological examination showed no evidence of congestion in any of these rats. Examination of kidneys from groups 5 and 6 demonstrated a characteristic dark discoloration in the inner stripe of the outer medulla. This lesion, clearly visible to the naked eye, was confirmed histologically to be caused by red cell packing in the peritubular capillaries of the inner stripe of the outer medulla. In group 4 rats, the cortex, inner and outer stripe, and inner medulla were of normal macroscopic appearance.

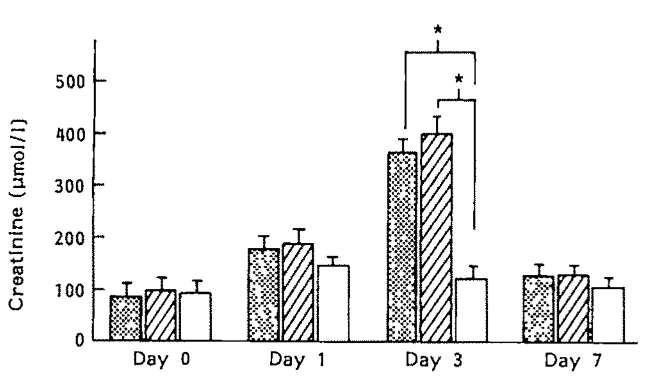

Figure 1 *Mean(s.e.m.) serum creatinine levels after 45-min ischaemia in rats given 0·9 per cent saline (▒), 3 per cent saline (■) or sodium bicarbonate (□).* *P < *0·001 (one-way analysis of variance)*

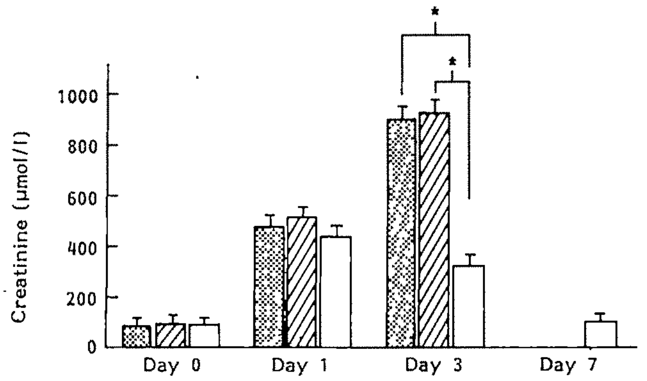

Figure 2 *Mean(s.e.m.) serum creatinine levels after 90-min ischaemia in rats given 0·9 per cent saline (□), 3 per cent saline (■) or sodium bicarbonate (□).* *P < *0·001 (one-way analysis of variance)*

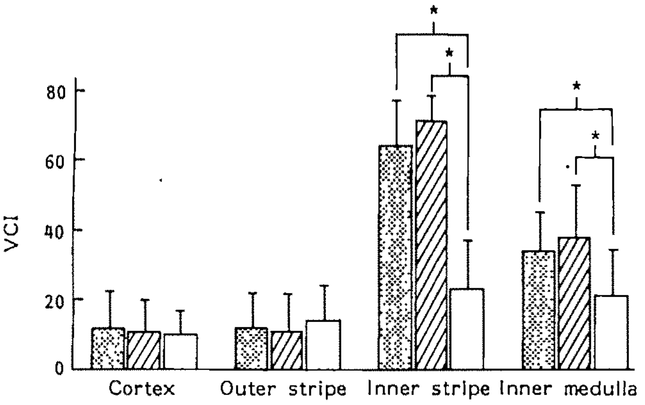

Figure 3 *Mean(s.e.m.) vascular congestion index (VCI) after 90-min ischaemia in rats given 0·9 per cent saline (▒), 3 per cent saline (■) or sodium bicarbonate (□).* *P < *0·001 (one-way analysis of variance)*

Histological examination demonstrated that vascular congestion was most marked in the inner stripe of the medulla in rats from groups 5 and 6. This congestion was absent in animals from group 4. Measurement of the VCI in control and test kidneys showed similar cortical and outer stripe staining in all three groups (*Figure 3*). The VCI for the inner stripe and inner medulla was significantly less in the bicarbonate-treated animals compared with both saline groups and in the 3 per cent saline group compared with controls ($P < 0·001$). The separate analysis of variance at each time gave differences that were significant even after Bonferroni correction for the multiple tests over time, making it unlikely that the results are artefactual.

Discussion

A characteristic series of changes occurs in the kidney after a significant period of ischaemia followed by reperfusion. A marked decrease in glomerular filtration and inner medullary blood flow is seen, with a relative preservation of cortical and total renal blood flow[20–22]. As early as 10 min after recirculation, the peritubular capillaries of the inner stripe of the outer medulla become packed with red blood cells[20]. Because the exact course of ischaemic damage to the kidney is incompletely understood, many protective agents have been used. Mannitol prevents ischaemia induced by cell swelling[1,11,13], and inosine may act by maintaining levels of purine nucleotides during ischaemia, allowing more rapid synthesis of adenosine 5′-triphosphate following reflow[12]. A direct vascular effect of inosine may also be involved[1,20]. Oxygen-derived free radicals may be important in the ischaemia–reperfusion injury[9,10]. Cell swelling, increased capillary permeability and medullary hyperaemia could be produced by the excessive generation of oxygen free radicals following re-establishment of the renal circulation.

Sodium bicarbonate has a protective effect in various forms of renal injury[17,19] but there are few data on its method of action and in particular on the potential benefit of a single prophylactic dose administered immediately before elective surgical ischaemia. In the first study[12] on the effects of bicarbonate on ischaemic renal injury, it was postulated that ammonia accumulation during ischaemia may cause post-ischaemic renal injury and that prevention of ammonia formation by urinary alkalinization might be protective. The possibility that ammonia might injure the kidney arose from the observation that toxic levels accumulate in the kidney and renal vein during ischaemia, produced by the action of the glutaminase enzyme system in the tubular cells at the corticomedullary junction. This enzyme converts glutamine to glutamic acid, leading to production of free ammonia. During ischaemia, glutaminase is not initially inhibited and production of ammonia continues, leading to toxic levels. Ammonia is

Table 1 *Blood pH and bicarbonate levels 3 h after pretreatment and urine pH and sodium excretion levels 24 h after pretreatment*

	Blood		Urine	
Pretreatment	pH	Bicarbonate level (mmol/l)	pH	Sodium excretion (mmol per 24 h)
Sodium bicarbonate	7·39(0·01)*	34·2(1·3)*	7·1(0·3)*	381·5(49·2)†
0·9% saline	7·22(0·22)	26·5(2·0)	6·2(0·4)	126·2(19·1)
3% saline	7·24(0·03)	27·1(1·9)	6·1(0·2)	366·0(37·0)†
Controls	7·25(0·02)	25·4(6·4)	6·4(0·4)	98·7(19·0)

Values are mean(s.e.m.). *$P < 0·01$ (sodium bicarbonate *versus* both saline groups); †$P < 0·001$ (sodium bicarbonate and 3 per cent saline *versus* 0·9 per cent saline); one-way analysis of variance nephrotoxic[23,24], causing inhibition of renal uptake of oxygen and *p*-aminohippuric acid and reducing renal creatinine clearance. Urinary alkalinization inhibits the main part of the glutaminase enzyme system and prevents potentially toxic effects of ammonia accumulation during ischaemia[12]. The present study shows that the effect is a local renal one, confirms that systemic alkalosis is not required and indicates that the protective effect is not based on volume expansion or sodium loading.

It has been shown[4–8] that postischaemic renal failure is associated with a medullary perfusion defect that occurs following reperfusion of the ischaemic kidney. This lesion, which is caused by red blood cell trapping in the peritubular capillaries of the inner stripe of the outer medulla, was prevented in rats treated with 8·4 per cent sodium bicarbonate. The prevention of this lesion is associated with a significant improvement in postischaemic renal function, which appears to result from maintenance of inner medullary vascular perfusion[8]. Oxygen free radical scavenging agents also diminish the severity of this vascular lesion[10] and there may be a connection between these observations. Radical generation is dependent on the action of enzymes such as the protease that converts xanthine dehydrogenase into xanthine oxidase, which in turn converts hypoxanthine to xanthine along the pathway of free radical production. The activity of the ammonia-generating enzyme system and the activity of free radical-generating enzymes may be inhibited by alkalinization of the bathing tubular fluid. This hypothesis is currently the subject of further investigation.

References

1. Flores J, Di Bona DR, Beck CH, Leaf A. The role of cell swelling in ischaemic renal damage and the protective effect of hypertonic solute. *J Clin Invest* 1972; **51**: 118–26.
2. Tanner GA, Stein Hausen M. Tubular obstruction in ischaemia induced acute renal failure in the rat. *Kidney Int* 1976; **10**: S65–73.
3. Frega NS, Di Bona DR, Gunther B, Leaf A. Ischaemic renal injury. *Kidney Int* 1976; **10**: S17–25.
4. Arendshorst WJ, Finn WF, Gottschalk CW. Micropuncture study of acute renal failure following temporary renal ischaemia in the rat. *Kidney Int* 1976; **10**: 100–6.
5. Torhorst J, de Rougemont D, Brunner FP, Thiel G. Morphology of the renal medulla in ischaemic acute renal failure. *Nephron* 1982; **31**: 296–300.
6. Thiel G, de Rougemont D, Friz W, Mason JF, Torhorst J. The role of reduced medullary perfusion in the genesis of acute ischaemic renal failure. *Nephron* 1982; **31**: 321–3.
7. Mason J, Torhorst J, Welsch J. Role of the medullary perfusion defect in the pathogenesis of ischaemic renal failure. *Kidney Int* 1984; **26**: 283–93.
8. Lennon GM, Ryan PC, Gaffney E, Fitzpatrick JM. Changes in regional renal perfusion following ischaemia/reperfusion injury to the rat kidney. *Urol Res* 1991; **19**: 259–64.
9. Hanson R, Gustafsson B, Jonsson O *et al.* Effect of xanthine oxidase inhibition on renal circulation after ischaemia. *Transplant Proc* 1982; **14**: 41–8.
10. Canavese C, Stratta P, Vercellone A. The case of oxygen free radicals in the pathogenesis of ischaemic acute renal failure. *Nephron* 1988; **49**: 9–15.
11. de Rougemont D, Brunner FP, Torhorst J, Wunderlich PF, Thiel C. Superficial nephron obstruction and medullary congestion after ischaemic injury: effect of protective treatments. *Nephron* 1982; **31**: 310–18.
12. Fernando AR, Griffiths JR, O'Donoghue EPN *et al.* Enhanced preservation of the ischaemic kidney with inosine. *Lancet* 1976; **i**: 555–9.
13. Burke TJ, Cronin RE, Duchin KL, Peterson LN, Schrier RW. Ischaemia and tubule obstruction during acute renal failure in dogs: mannitol in protection. *Am J Physiol* 1980; **F238**: 315–23.
14. Burke TJ, Arnold PE, Schrier RW. Prevention of ischaemic acute renal failure with impermeant solutes. *Am J Physiol* 1983; **F244**: 646–9.
15. Fitzpatrick JM, Monson JRT, Gunter PH, Watkinson LE, Wickham JEA. Renal accumulation of ammonia: the cause of post-ischaemic function loss and the blue line. *Br J Urol* 1982; **54**: 608–12.
16. Atkins JL. Effect of sodium bicarbonate preloading on ischaemic renal failure. *Nephron* 1986; **44**: 70–4.
17. Eneas JF, Schoenfield PY, Humphreys MH. The effect of an infusion of mannitol–sodium bicarbonate on the clinical course of myoglobinuria. *Arch Intern Med* 1979; **139**: 801–5.
18. Michaelson M, Taitelman U, Bshouty Z, Bar-Joseph G, Bursztein S. Crush syndrome: experience from the Lebanon War 1984. *Isr J Med Sci* 1984; **20**: 305–7.
19. Kopp KF, Thul GM. Prophylaxis and emergency treatment of acute renal failure by acute intravenous bicarbonate loading. In: Eliahou H, ed. *Acute Renal Failure. Proceedings of the Tel Aviv Satellite Symposium, 8th International Society of Nephrology Meeting*. New York: Karger, 1982: 181–5.
20. Wolgast M, Karlberg L, Kullskog O, Norlen BJ, Nygren K, Ojteg G. Haemodynamic alterations in ischaemic acute renal failure. *Nephron* 1982; **31**: 301–3.
21. Karlberg L, Norlen BJ, Ojteg G, Wolgast M. Impaired medullary circulation in post-ischaemic acute renal failure. *Acta Physiol Scand* 1983; **118**: 11–17.
22. Karlberg L, Kallskog O, Norien BJ, Wolgast M. Post-ischaemic renal failure. Intrarenal blood flow and functional characteristics in the recovery phase. *Acta Physiol Scand* 1982; **115**: 1–10.
23. Wickham JEA, Sharma GP. Endogenous ammonia formation in experimental renal ischaemia. *Lancet* 1965; **i**: 195–8.
24. Preuss HG, Murdaugh HV. The toxic effect of ammonia on renal cortical tubule function *in vitro*. *J Lab Clin Med* 1968; **71**: 561–72.

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Simultaneous dynamic electromyographic proctography and cystometrography

The rectum and bladder share a common origin and work in harmony; disturbance in one may lead to a similar problem in the other. The two have, however, not previously been investigated dynamically and simultaneously. A new system has been devised allowing dynamic integrated electromyographic proctography to be performed simultaneously with cystometrography in 41 patients (28 women and 13 men). Of 16 women with chronic constipation who underwent the combined study, ten were shown to have obstructed micturition. Eight of these ten women exhibited an inappropriate contraction of the puborectalis muscle during micturition, compared with one of the six with normal micturition (P = 0·02). *Of the patients with obstructed micturition, seven of eight women with a rectocele also had anismus, compared with none of four women with a rectocele among those who were able to micturate normally* (P = 0·02). *Eight of the ten women with obstructed micturition thus had a proctological abnormality that explained the urological symptoms. Of 12 women with idiopathic faecal incontinence who underwent the combined study, eight were shown to have genuine stress incontinence of urine. In seven of these the severity was shown to be of type 2a or greater, indicating that pelvic floor dysfunction may be the causal factor of both rectal and urinary symptoms. The combined study shows abnormalities in one system that could explain similar symptoms in the other.*

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The bladder and rectum share a common embryological origin in the cloaca. Not surprisingly, the motor nerve supply of each arises from the pelvic parasympathetic outflow (S2–S4). In addition, the external anal sphincter and external urethral striated sphincter are both innervated by the pudendal nerve. In health the bladder and rectum function in harmony. Both systems are, however, usually viewed as separate clinical entities: the effect that one may have on the other is rarely considered. Recent evidence suggests that a disorder in one of these systems may be accompanied by a similar problem in the other[1–4]. Despite such data, bladder and anorectal studies are invariably performed separately, by different specialists on different occasions, even when patients complain of both urinary and rectal symptoms. Such isolated investigation is unlikely to detect any influence of the rectum on bladder function.

A new technique has therefore been developed, in which rectal and vesical function are monitored simultaneously and dynamically, using simultaneous dynamic integrated electromyographic (EMG) proctography and cystometrography. This combined technique enables simultaneous manometric monitoring of the rectum and bladder, electromyography of the puborectalis muscle, and radiological visualization not only of the rectum at rest and during defaecation, but also of the bladder during filling and micturition.

Patients and methods

Patients

All patients who underwent the combined study complained of both proctological and urological symptoms. A full evaluation of the bowel, urological and past medical history was made in each. Women were also questioned in detail on past gynaecological and obstetric history.

A total of 41 patients (28 women, 13 men) underwent anorectal manometry, proctometrography and the combined study. Patients were divided into two groups: 23 with constipation and urinary symptoms (16 women of mean(s.e.m.) age 48·1(3·8) years, seven men of mean(s.e.m.) age 55·1(5·4) years) and 18 with faecal incontinence and urinary symptoms (12 women of mean(s.e.m.) age 58·4(4·5) years, six men of mean(s.e.m.) age 49·0(5·5) years).

Of the 16 constipated women, ten had to digitate to evacuate the rectum, all 16 had a feeling of incomplete evacuation after defaecation, and 15 regularly used laxatives. Eight of the women had obstructed defaecation, four had constipation due to slow transit and two had a combination of these two factors. In the two remaining women the aetiology was unknown. Of the seven constipated men studied, four had to digitate to evacuate, six had a feeling of incomplete evacuation after defaecation, and four used laxatives regularly. Four of the men had obstructed defaecation, two had constipation due to slow transit, and one suffered from a combination of these two factors.

Of the 12 faecally incontinent women studied, six had a history of constipation and ten were multiparous. Six were incontinent to solid stool and six to liquid only. Eleven of the women were thought to have neurogenic faecal incontinence, the remaining patient having a history of traumatic tear during labour. Of the six faecally incontinent men studied, five were incontinent to solid and liquid faeces and one to liquid only. Two of these patients had a record of constipation and three had a neurological history (spina bifida, transverse myelitis and dystrophia myotonica).

The duration of proctological and urological symptoms and type of the latter are shown in *Tables 1* and *2* respectively. Constipated women had significantly more hesitancy and straining than faecally incontinent women ($P = 0{\cdot}02$), suggesting that the former were more likely to have symptoms of obstructed micturition. Eight of the 16 constipated women had symptoms of stress incontinence of urine, compared with eight of the 12 faecally incontinent women (P not significant).

Ethical approval was granted by the Tower Hamlets Ethical Approval Committee.

Methods

Anorectal manometry and proctometrography. Anorectal manometry was performed by a station pull-through technique using a water-perfused balloon mounted on a catheter (external diameter

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2·5 mm), with the patient in the left lateral position[5]. The water-perfused system was connected to a pressure transducer, which was linked to an MX 4P-145 amplifier and 5045-50 recorder (all from Lectromed (Oromed), Welwyn Garden City, UK). Maximum basal, squeeze and squeeze increment pressures were recorded. Rectal compliance, minimum perceived volume, defaecatory desire volume, and maximum tolerated volume were each measured by balloon proctometrography[6].

Combined study and measurement of anorectal angles. This study was carried out in the anorectal radiology suite. Each patient was asked to micturate to empty the bladder. With the patient lying in the left lateral position on the fluoroscopic screening couch 60 ml barium sulphate suspension was introduced into the rectum through a 12-Fr Foley catheter. The catheter was held in place by inflating a 5-ml balloon and by placing a small pair of arterial forceps across the catheter at the anal verge. Anorectal angles were measured at rest, and during squeeze and strain.

After the anorectal angles had been measured the catheter was removed, but the barium suspension was left in place so that the rectum could be visualized during subsequent bladder filling. With the patient still in the left lateral position, two fine-wire EMG electrodes (polytetrafluoroethylene-coated stainless steel; Clark Electromedical Instruments, Reading, UK) were inserted through a sterile needle into the puborectalis muscle under local anaesthesia (1 ml 1 per cent subcutaneous lignocaine)[7]. The tip of the needle was inserted into the perianal skin at 3 o'clock (with reference to the anus: anterior is 12 o'clock) and directed by a finger in the rectum posteriorly and medially into the puborectalis. The two wire electrodes were fixed with adhesive strapping so that they did not become dislodged during the study; they were connected to a Neurolog System filter and Medelec amplifier (Vicker's Health Care, Basingstoke, UK). A microtipped pressure transducer of external diameter 2·2 mm (Gaeltec, Isle of Skye, UK) was then introduced 10 cm into the rectum and taped to the perianal skin to prevent movement. The patient was then turned to the supine position. Using aseptic technique a second Gaeltec microtipped pressure transducer (external diameter 2·0 mm) and an 8-Fr Nelaton filling catheter (Pennine Healthcare Products, Derby, UK) were introduced into the bladder transurethrally. The catheters were strapped into place and any residual urine on catheterization noted. The two Gaeltec catheters were then connected to a pair of 57B pressure recorders (Gaeltec). Each Gaeltec catheter was individually calibrated against a 50-cm water column before each study. The patient was then screened fluoroscopically to check the position of each catheter. The combined study was recorded on videotape using a Sony Vo 5800PS videorecorder (Sony, Tokyo, Japan).

The EMG amplifier, pressure recorders, fluoroscopic screening and videorecorder were all integrated using an Archimedes 310 computer (Acorn, Cambridge, UK) with custom-built software.

A filling cystometrogram was then performed, infusing Isopaque Cysto 100 mg iodine ml^{-1} (Nycomed, Birmingham, UK) at a rate of 100 ml min^{-1}. First sensation, volume causing desire to micturate, end filling pressure and evidence of detrusor instability were all noted. The patient was then transferred to the erect position, turned to an oblique angle and asked to cough repeatedly. Any bladder neck beaking, descent or leak of urine due to stress incontinence of urine was noted.

The patient was then returned to the left lateral position. A barium–porridge mixture (one part barium sulphate, two parts porridge oats (J. Sainsbury, London, UK), three parts water) that had been kept in a water bath at 37°C and previously weighed was injected into the rectum through a proctoscope. Enough mixture was introduced to give a strong desire for rectal evacuation (up to 120 ml). The patient then sat on a radiolucent water-filled commode and was monitored fluoroscopically from the lateral position. Each patient was initially requested to cough and any faecal incontinence noted. The patient was next requested to micturate. If unable to do so they were requested to defaecate. Radiological abnormalities such as a rectocele, intussusception and full-thickness prolapse were recorded simultaneously with intrarectal pressure and puborectalis EMG activity. The patient was finally requested to micturate again. Intrarectal pressure, intravesical and subtracted detrusor pressure were recorded simultaneously with any radiological abnormalities and with puborectalis EMG activity. At the end of the investigation the barium–porridge mixture that had been voided was weighed.

During the evacuation phase of the investigation, privacy was ensured by placing large curtain screens around the patient and by dimming the lights in the radiology suite. Silence was maintained while the patient was evacuating, to avoid any distraction.

Definition of terms used in the combined study

Genuine stress incontinence of urine. This was defined as incontinence of urine occurring when intravesical pressure exceeded the maximum urethral pressure in the absence of detrusor activity[8]. The degree of stress incontinence found in the present patients during the combined study was classified according to the scheme described by Green[9] and modified by Blaivas[10]. These types are:

> Type 0. There was a good history of stress incontinence. During videourodynamic study the vesical neck and proximal urethra were closed at rest, being situated at or above the superior margin of the pubic symphysis, and during stress, although the vesical neck and proximal urethra were open, no incontinence was demonstrated.
>
> Type 1. The vesical neck was closed at rest, being situated at or above the inferior margin of the symphysis pubis. During stress with increased abdominal pressure, the vesical neck and proximal urethra were seen to open and descend <2 cm, urinary incontinence being demonstrated.
>
> Type 2a. The vesical neck was closed at rest and above the inferior margin of the symphysis pubis. During stress the vesical neck and urethra descended >2 cm and during increased abdominal pressure urinary incontinence was demonstrated. A cystocele was also present.
>
> Type 2b. At rest the vesical neck was closed but situated below the inferior margin of the symphysis pubis. During stress there was further descent, the proximal urethra opened and incontinence was demonstrated.
>
> Type 3. At rest the vesical and proximal urethra were open despite the absence of a detrusor contraction. There was obvious leakage of urine, which was either gravitational or associated with a minimal increase in intravesical pressure.

Table 1 *Duration of symptoms*

	Mean(s.e.m.) duration (years)	
	Proctological	Urological
Constipated patients		
Men	7·4(2·2)	8·0(2·4)
Women	9·0(3·3)	5·2(1·1)
Faecally incontinent patients		
Men	8·1(2·5)	8·3(2·6)
Women	4·8(2·7)	2·4(1·8)

Table 2 *Type of urological symptoms*

	Frequency	Nocturia	Strain and hesitancy	Dysuria	Genuine stress incontinence	Urgency
Constipated patients						
Women ($n = 16$)	13	14	12*	8	8	5
Men ($n = 7$)	4	5	5	4	0	3
Faecally incontinent patients						
Women ($n = 12$)	9	9	4	2	8	5
Men ($n = 6$)	3	2	1	0	2	3

*$P = 0{\cdot}02$ (constipated *versus* faecally incontinent women, Fisher's exact test)

Detrusor instability. This was defined as a demonstable detrusor contraction occurring either spontaneously or on provocation, during the filling phase of cystometrography, while the patient was attempting to inhibit micturition[11].

Anismus. This has been defined as an inappropriate contraction of the puborectalis during defaecation[12]. Such a definition is, in our view, imprecise[13]. Anismus was defined in the present study when the following criteria were met: (1) recruitment of the puborectalis by EMG recording of ≥ 50 per cent; (2) increase in intrarectal pressure during straining by ≥ 50 cmH$_2$O from the resting rectal pressure to the maximum voiding pressure; and (3) period of straining during which inappropriate EMG activity of the puborectalis was recorded of ≥ 2 min.

Radiation dosage used during the combined study

Calculation of the radiation dosage during the combined study was made by the Department of Medical Physics, The Royal London Hospital. A patient weighing 72 kg undergoing fluoroscopic screening for 2 min received a dose of 6·0 mSv. (A patient having a barium enema receives 7·7 mSv and one undergoing intravenous urography 4·4 mSv.)

Statistical analysis

Differences in the incidence of findings between two groups were analysed by Fisher's exact test. Numerical values are expressed as the mean(s.e.m.) with differences between two groups being assessed by Student's unpaired *t* test.

Results

Anorectal manometry

There were no significant differences in anorectal pressure between patients with constipation and those with faecal incontinence (*Table 3*). Analysis by sex also showed no difference, although women had lower values for all three parameters studied.

Table 3 *Anorectal manometry*

	Constipated patients	Faecally incontinent patients
Maximum resting pressure (cmH$_2$O)	61(6·7)	50(7·1)
Maximum attained pressure (cmH$_2$O)	102(11·0)	92(12·4)
Maximum squeeze increment (cmH$_2$O)	43(7·4)	42(6·9)

Values are mean(s.e.m.)

Table 4 *Rectal compliance and sensation*

	Constipated patients	Faecally incontinent patients
Compliance (ml cmH$_2$O^{-1})	6·1(0·7)	5·9(0·7)
First sensation volume (ml)	150·1(23·4)	123·9(13·1)
Defaecatory desire volume (ml)	239·1(27·2)	227·1(26·8)
Maximum tolerated volume (ml)	443·8(130·0)	327·4(35·8)

Values are mean(s.e.m.)

Rectal compliance and first sensation, defaecatory desire and maximum tolerated volumes during proctometrography were not significantly different in constipated and faecally incontinent patients (*Table 4*). Again there was no sex difference.

Anorectal angles

Anorectal angles at rest, squeeze and strain were significantly greater in incontinent than in constipated women (*Table 5*). The difference in anorectal angles between the constipated and faecally incontinent men was not statistically significant.

Combined study

Rectal voiding. The mean(s.e.m.) fraction of artificial stool voided by the constipated men was significantly less than that voided by the faecally incontinent men (51·1(10·3) *versus* 95·7(1·8) per cent, $P = 0·004$). No significant difference was found between the constipated and faecally incontinent women (63·1(8·7) *versus* 82·9(7·5) per cent, $P = 0·09$).

The mean(s.e.m.) initial and maximum rectal pressures during evacuation in the constipated women were 36·2(3·9) and 99·1(9·4) cmH$_2$O respectively. Initial and maximum rectal pressures in faecally incontinent women were 35·9(6·0) and 108·2(20·4) cmH$_2$O respectively. These values were not significantly different between the two groups ($P = 0·9$ and $P = 0·7$). The mean(s.e.m.) initial and maximum rectal pressures during evacuation were not significantly different between the constipated and faecally incontinent men at 33·6(3·0) *versus* 45·7(5·4) cmH$_2$O ($P = 0·08$) and 145·9(20·7) *versus* 123·5(21·3) cmH$_2$O ($P = 0·5$) respectively.

Micturition: constipated patients. During the dynamic studies it became apparent that the patients micturated by two different mechanisms, either by generating a true detrusor contraction or by raising intra-abdominal pressure. Six constipated women micturated by generating a true detrusor contraction and ten did so using raised intra-abdominal pressure. Of the constipated men, one micturated by detrusor contraction and six by intra-abdominal straining. The mean(s.e.m.) maximal intra-abdominal pressures (recorded as rectal pressure) for the female and male constipated patients attained during micturition were 118·0(16·1) and 155·0(9·6) cmH$_2$O respectively. These values are all considerably higher than the accepted normal for maximal pressure during micturition[13]. The mean(s.e.m.) maximum pressures recorded during micturition by generation of a true detrusor contraction were 42·5(7·3) cmH$_2$O for the women and 48·0 cmH$_2$O for the man.

Figure 1 shows the proctological findings during micturition. Anismus was significantly more common in women micturating by raised intra-abdominal pressure than in those who did so by detrusor pressure ($P = 0·02$). No significant difference was found in the numbers with rectocele or intussusception in the two groups. No difference in radiological abnormalities was demonstrated between men who micturated by abdominal strain and the one doing so by detrusor contraction.

An association was found between rectocele and anismus in women who micturated by abdominal straining: of eight

Table 5 *Anorectal angles*

	Women			Men		
	Constipated	Faecally incontinent	*P**	Constipated	Faecally incontinent	*P**
Rest (°)	90·9(3·5)	111·9(4·5)	0·001	87·5(6·9)	106·8(7·6)	0·08
Squeeze (°)	80·1(3·2)	99·4(5·9)	0·002	79·9(5·9)	98·6(5·4)	0·06
Strain (°)	101·5(4·2)	121·9(3·8)	0·001	102·5(6·8)	118·5(7·0)	0·13

Values are mean(s.e.m.). *Student's unpaired *t* test

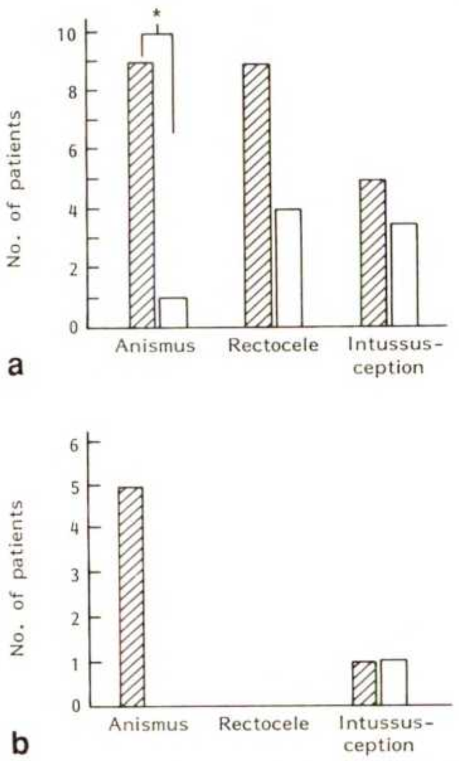

Figure 1 *Proctological abnormalities found during micturition in constipated* **a** *women and* **b** *men micturating by abdominal strain* (▨) *or detrusor contraction* (☐). *P = 0·02 (*Fisher's exact test*)

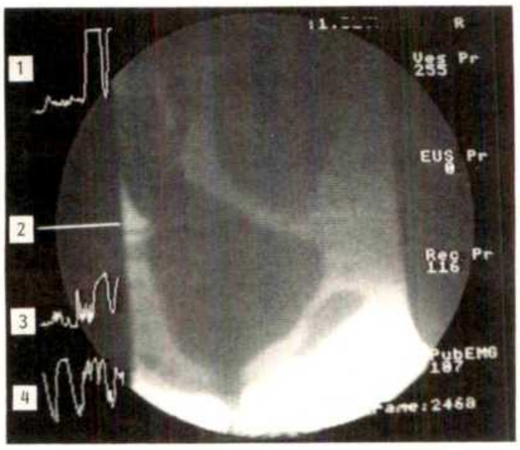

Figure 2 *The appearance of a large rectocele during defaecation (rectum posteroinferior, bladder anterosuperior). Tracing 1 represents intravesical pressure, 3 shows intrarectal pressure and 4 shows puborectalis electromyography. (Tracing 2 was not used during the investigation)*

patients who micturated by abdominal straining, seven had anismus. In contrast, there was no anismus in the four women with a rectocele who micturated by detrusor pressure. This difference was statistically significant ($P = 0{\cdot}02$). *Figure 2* is taken from the videorecording of a female patient during defaecation. The intrarectal pressure is seen to increase (trace 3) and there is a paradoxical EMG recruitment of the puborectalis (trace 4). A large rectocele can be seen to develop on the anterior rectal wall. *Figure 3* shows a recording of the same woman during micturition. The intravesical pressure (trace 1) can be seen to be grossly raised during attempted micturition, and a paradoxical EMG recruitment of the puborectalis is also noted (trace 4). The large rectocele first noted during defaecation is clearly seen to be advancing further in the anterior direction, causing the bladder neck and urethra to become angulated and obstructing bladder emptying.

Micturition: faecally incontinent patients. Micturition was achieved in a similar pattern to that in constipated patients, either by a true detrusor contraction or by raising intra-abdominal pressure. The raised intra-abdominal pressures generated by both the female and male patients were again considerably higher than the upper limit of normal for maximum micturition voiding pressures[14]. Eight women micturated by generating a detrusor contraction, mean(s.e.m.) maximum detrusor pressure 42·1(7·0) cmH$_2$O, four by high intra-abdominal pressure, mean(s.e.m.) 122·0(11·6) cmH$_2$O. Of the men, three micturated by generating a detrusor contraction, mean(s.e.m.) pressure 41·7(13·0) cmH$_2$O and three by high intra-abdominal pressure, mean(s.e.m.) 140·4(30·5) cmH$_2$O.

Figure 4 shows the proctological findings during micturition in faecally incontinent patients. There was no statistical difference in the incidence of anismus, rectocele or intussuscep-

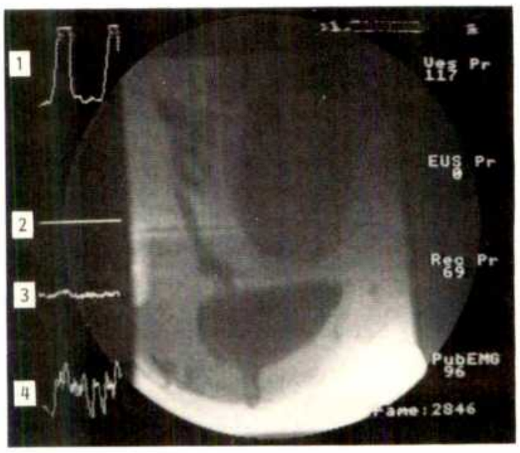

Figure 3 *Micturition in the same patient as in* Figure 2. *The rectocele persists and enlarges during micturition, leading to a distortion in the anatomy of the bladder neck and urethra. It is responsible for extrinsic obstruction to the urethra. (Tracing 2 was not used during the investigation)*

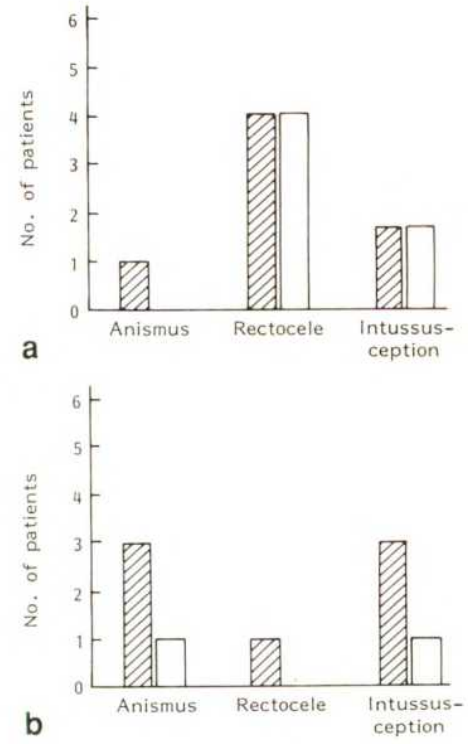

Figure 4 *Proctological abnormalities found during micturition in faecally incontinent* **a** *women and* **b** *men micturating by abdominal strain* (▨) *or detrusor contraction* (☐)

tion in patients micturating by detrusor pressure and those micturating by intra-abdominal pressure.

Genuine stress incontinence in female patients. Eight of the 16 women with chronic constipation exhibited genuine stress incontinence on coughing during cystometrography, compared with eight of the 12 with faecal incontinence (P not significant). On assessing the degree of stress incontinence in both groups it was found that seven of the eight faecally incontinent women had incontinence of type 2a or worse, compared with one of the eight women with chronic constipation ($P = 0{\cdot}02$).

Discussion

Anorectal manometry and balloon proctometrography, while allowing accurate measurements of anal sphincter pressures and rectal compliance and capacity, have the disadvantage of being static isolated investigations. Dynamic proctography, while enabling a more synchronized approach to the study of anorectal function, does not allow any recognition of bladder dysfunction or of any possible effect that the bladder may exert on anorectal activity. Likewise, modern urodynamics[15–17], while enabling the accurate diagnosis of lower urinary tract dysfunction[18–20], cannot recognize the influence of rectal dysfunction on the urological problem being investigated. Neither do any of these sets of investigations enable the recognition of dual pathologies. However, since the combined study described monitors bladder and rectal function simultaneously, it is possible to observe the effect of dysfunction of one system on the other.

Previous studies have tried to correlate rectal and bladder dysfunction. Preston and Lennard-Jones[1], and Varma and Smith[3] noted urological symptoms in women with idiopathic constipation. Kerrigan *et al.*[4] investigated patients with idiopathic constipation and reported impaired urethrovesical function. Bannister *et al.*[2] investigated urological abnormalities in women with severe constipation. In the latter two studies, however, anorectal and urological symptoms were investigated separately.

Others have tried to correlate rectal and bladder dysfunction, but in a non-integrated way. Godec *et al.*[21] studied the effect on the voiding reflex of electrical stimulation of the rectal ampulla by six surface electrodes. Their results remain questionable because the method employed was unphysiological. Abdel-Rahmen *et al.*[22] performed 'urorectodynamics' on patients with colonic inertia, attempting to correlate rectal and bladder function by simultaneous urodynamics and anorectal manometry. However, there was no radiological visualization of either rectum or bladder, and no electrophysiological measurement. This was therefore in reality a non-integrated approach that involved only one aspect of rectal and bladder physiology and did not correlate the results with function in either organ. Snooks *et al.*[23] studied 40 women with neurogenic faecal incontinence, 20 of whom also had stress urinary incontinence. Electrophysiological studies, anorectal manometry and measurement of perineal descent were used in isolation from each other; no urodynamics were performed.

Hence, although previous studies have attempted to assess dysfunction in both the bladder and rectum, none has addressed the problem in a dynamic synchronized manner. The present study has shown that patients suffering from both anorectal and bladder dysfunction can successfully undergo dynamic investigation of both systems simultaneously. The investigation has the advantage of not only being dynamic in nature but also allowing for the synchronous visualization of the rectum and bladder.

There is a subgroup of constipated women with obstructed micturition whose urological symptoms are secondary to proctological abnormalities. These patients micturate using high intra-abdominal pressures that appear to be secondary to either a large rectocele, inappropriate contraction of the puborectalis, or both. The radiological and physiological abnormalities demonstrated in these patients could have been detected only using the combined study: they would not have been discovered through urodynamics and cystoscopy alone. These results have therapeutic implications, for correction of the underlying proctological abnormalities in these patients may correct the urological difficulties. Two of the younger constipated women have undergone repair of the rectocele; both report a subjective improvement in symptoms, although neither has yet been investigated after operation.

In the group of faecally incontinent women with genuine stress incontinence of urine, the results obtained from the combined study suggest that double incontinence may arise from a common aetiology. Cystometrography demonstrated that the grade of stress incontinence in faecally incontinent women was more severe than in constipated women. The anorectal angles at rest, squeeze and strain in the former were significantly wider than in the latter. The greater descent of the pelvic floor and more obtuse anorectal angle in the faecally incontinent women suggest that both faecal and urinary incontinence in this group may be due to pelvic floor denervation, although it must be noted that the anorectal manometry in these patients revealed reasonable resting and squeeze pressures. This may be partially explained by the fact that only half of the group was incontinent to solid stool, the rest being incontinent to liquid faeces only, thus having a milder form of incontinence. These findings have implications for the treatment of urinary incontinence in these patients. Recent evidence from Laurberg *et al.*[24] suggests that there may be progression of neurogenic damage to the pelvic floor muscles after postanal repair in patients with faecal incontinence; this may be responsible for the poor functional results after this operation. It may be extrapolated that similar poor results might be expected in the long term after colposuspension in patients with neurogenic damage to the pelvic floor, because the bladder neck would be buttressed and supported by similarly denervated musculature and paravaginal tissue. Indeed, although initial success rates of 90 per cent with the Burch colpususpension have been reported[25], with long-term follow-up[26] this may fall to 44 per cent. It has also been observed that women may suffer recurrent stress incontinence after a protracted symptom-free period following an intact repair[27].

The combined study is obviously a major undertaking for any patient; it requires them to perform acts in public that would normally take place in the privacy of a home environment. However, with screening around the patient, maintenance of silence during evacuation studies, and a compassionate and sympathetic attitude, useful data can be obtained. These data may be clinically applicable to the patient's underlying pathophysiological abnormalities. A combined and integrated investigation of proctological and urological symptoms may provide information that cannot be obtained in any other way.

Acknowledgements

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References

1. Preston DM, Lennard-Jones JE. Severe chronic constipation of young women: 'idiopathic slow transit constipation'. *Gut* 1986; **27**: 41–8.
2. Bannister JJ, Lawrence WT, Smith A *et al.* Urological abnormalities in young women with severe constipation. *Gut* 1988; **29**: 17–20.
3. Varma JS, Smith AN. Neurophysiological dysfunction in young women with intractable constipation. *Gut* 1988; **29**: 963–8.
4. Kerrigan DD, Lucas MG, Sun WM *et al.* Idiopathic constipation associated with impaired urethrovesical and sacral reflex function. *Br J Surg* 1989; **76**: 748–51.

5. Neill ME, Parks AG, Swash M. Physiological studies of the pelvic floor in idiopathic faecal incontinence and rectal prolapse. *Br J Surg* 1981; **68**: 531–6.
6. Varma JS, Smith AN. Reproducibility of the proctometrogram. *Gut* 1986; **27**: 288–92.
7. Womack NR, Williams NS, Holmfield JHM *et al.* A new method for the dynamic assessment of anorectal function in constipation. *Br J Surg* 1985; **12**: 994–8.
8. Hilton P. Urinary incontinence in women. *BMJ* 1987; **295**: 426–32.
9. Green TH, Thomas H Jr. The problem of urinary stress incontinence. *Obstetrical and Gynecological Survey* 1968; **23**: 603–34.
10. Blaivas JG. Classification of stress urinary incontinence. *Neurourology and Urodynamics* 1984; **2**: 103.
11. Hald T, Bates CP, Bradley WE *et al.* The standardisation of terminology of lower urinary tract function; a collation of reports from the standardisation committee of the International Continence Society. Glasgow: International Continence Society, 1984.
12. Preston DM, Lennard-Jones JE. Anismus in chronic constipation. *Dig Dis Sci* 1985; **30**: 413–18.
13. Roberts JP, Thorpe AC, Williams NS. Assessment of defective rectal evacuation by dynamic integrated proctography. *Br J Surg* 1991; **78**: 747A.
14. Abrahms P. The practice of urodynamics. In: Munday AR, Stephenson TP, Wein AJ, eds. *Urodynamics: Principles, Practice and Application.* 1st ed. Edinburgh: Churchill Livingstone, 1983: 76–92.
15. Bates CP, Whiteside BM, Turner-Warwick RT. Synchronous cine/pressure/flow/cystourethrography with special reference to stress and urge incontinence. *Br J Urol* 1970; **42**: 714–17.
16. Griffiths DJ. Urodynamic assessment of the bladder. *Br J Urol* 1977; **49**: 29–36.
17. Webster GD, Older RA. Videourodynamics. *Urology* 1980; **16**: 106–14.
18. McGuire EJ, Lytton B, Kohorn EI *et al.* The value of urodynamic testing in stress urinary incontinence. *J Urol* 1980; **124**: 256–8.
19. Bottacini MR, Gleason DM. Urodynamic norms in women. I. Normal *versus* stress incontinence. *J Urol* 1980; **124**: 659–62.
20. Haylen BT, Sutherst JR, Frazer MI. Is the investigation of most stress incontinence really necessary? *Br J Urol* 1989; **64**: 147–9.
21. Godec C, Giovanni A, Cass A. Electrical stimulation of the rectal ampulla causing reflex voiding. *J Urol* 1977; **117**: 770–2.
22. Abdel-Rahmen M, Topperier A, Duguay C *et al.* Urorectodynamics in patients with colonic inertia. *Urology* 1981; **18**: 428–32.
23. Snooks SJ, Barnes RPH, Swash M. Damage to the voluntary anal canal and urinary sphincter musculature in incontinence. *J Neurol Neurosurg Psychiatry* 1984; **47**: 1269–73.
24. Laurberg S, Swash M, Henry MM. Effect of postanal repair on progress of neurogenic damage to the pelvic floor. *Br J Surg* 1990; **77**: 519–22.
25. Stanton SL, Cardozo LD. Results of the culposuspension operation for incontinence and prolapse. *Br J Obstet Gynaecol* 1979; **86**: 693–7.
26. Galloway NTM, Davies N, Stephenson TP. The complications of culposuspension. *Br J Urol* 1987; **60**: 122–4.
27. Quinn MJ, Benyon J, Mortensen NNMcC *et al.* Vaginal endosonography in the post-operative assessment of colposuspension. *Br J Urol* 1989; **63**: 295–300.

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Effect of anorectal eversion during restorative proctocolectomy on anal sphincter function

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Twenty-six patients underwent restorative proctocolectomy with end-to-end ileal pouch–anal anastomosis, without resection of the anal mucosa, by the eversion technique. Before surgery patients underwent tests of anorectal function. These were repeated a median of 8 (range 3–21) months after operation. The median (range) maximum resting anal pressure was 93 (36–149) cmH$_2$O before and 71 (40–131) cmH$_2$O after operation (P = 0·002). The median (range) maximum squeeze pressure before operation was 136 (73–280) cmH$_2$O; it was 149 (69–290) cmH$_2$O afterwards (P not significant). The median (range) length of the anal sphincter was 3·5 (2·5–4·5) cm before and 3·5 (2·0–4·5) cm after operation (P not significant). Thresholds for sensation in the upper, middle and lower thirds of the anal canal before and after operation were, respectively, 8·7 versus *8·7, 6·8* versus *7·4 and 4·2* versus *6·2 mA (P not significant). All 26 patients were continent, although one experienced minor leakage. Function of the anal sphincter is not significantly impaired by eversion of the rectum and anus during restorative proctocolectomy.*

Restorative proctocolectomy with ileoanal anastomosis has become the procedure of choice in the elective surgical treatment of most patients with ulcerative colitis. Controversy exists as to whether the pelvic reservoir should be anastomosed endoanally to the internal anal sphincter at the dentate line (after stripping of the anal mucosa) or end to end, at a slightly higher level, without mucosal stripping. The end-to-end ileoanal anastomosis has been favoured because of its technical simplicity and better functional outcome[1,2]. One technical problem with the stapled end-to-end anastomosis is that the level of construction may be difficult to determine by the abdominal operator during the pelvic dissection. If the anastomosis is constructed too high, a cuff of inflamed rectal mucosa may remain and cause complications and an imperfect functional outcome. To facilitate construction of the anastomosis, the technique of eversion of the anorectal stump was devised so that the level of transection could be defined more accurately. Such a technique might, however, damage the anal sphincter or its nerve supply and impair continence[3–5]. This study investigated the effects of anorectal eversion on the function of the anal sphincter.

Patients and methods

A consecutive series of 13 men and 13 women was studied. Each patient had undergone restorative proctocolectomy for ulcerative colitis between December 1989 and April 1991. The median age was 36 (range 17–66) years. Each patient underwent end-to-end ileoanal anastomosis, without stripping of the anal mucosa. A quadruplicated (W) reservoir[6] was constructed in 23 patients and a duplicated (J) pouch[7] in three, 40 cm of distal ileum being utilized in each case.

Technique of anorectal eversion and end-to-end ileoanal anastomosis

The rectum was mobilized by close perimuscular dissection as far as the upper anal canal, then transected at mid-rectal level, stay sutures inserted and the anorectal stump everted from the anus. Strong distal traction on the anorectal stump provided a clear display of the dentate line and anal columns, and allowed a TA30 or TA55 (Auto Suture, Ascot, UK) linear stapling device to be placed accurately across the anorectal stump 1·5–2·0 cm above the dentate line. The anorectal sleeve was then transected at this level to produce a 'blind' anal stump, which returned to the pelvis when the stapler was removed. A Premium CEEA (Auto Suture) stapling device was used to fashion an end-to-end anastomosis approximately 1·0–1·5 cm above the dentate line.

Laboratory studies

Each patient underwent tests of anal sphincter function before operation and a median of 8 (range 3–21) months after operation or ileostomy closure. Anal pressure was measured by the station pull-through technique[1]. Sensation was tested by measuring threshold electrosensitivity of the anal mucosa[8]. The pouch–anal inhibitory reflex was assessed by inflating a balloon in the ileal reservoir with air and measuring the response of the anal sphincter. A 20 per cent decrease in pressure was taken to denote a positive reflex[9].

Clinical assessment of outcome

The quality of anal continence was assessed by monitoring: faecal leakage; anal soreness; the ability to defer defaecation; and the ability to discriminate between flatus and faeces and to release flatus safely without fear of faecal leakage and requirement for a toilet.

Statistical analysis

All group data are expressed as median (range). Groups were compared by use of the Wilcoxon matched-pairs signed rank test for paired data[10].

Results

Anal pressure

The median (range) maximum resting anal pressure was 93 (36–149) cmH$_2$O before and 71 (40–131) cmH$_2$O after operation ($P = 0{\cdot}002$). The median (range) maximum squeeze pressure was 136 (73–280) cmH$_2$O before surgery and 149 (69–290) cmH$_2$O afterwards (P not significant) (*Figure 1*).

Pressure profile of anal sphincter

The pressure profile of the anal sphincter before and after operation is illustrated in *Figure 2*. The median (range) length

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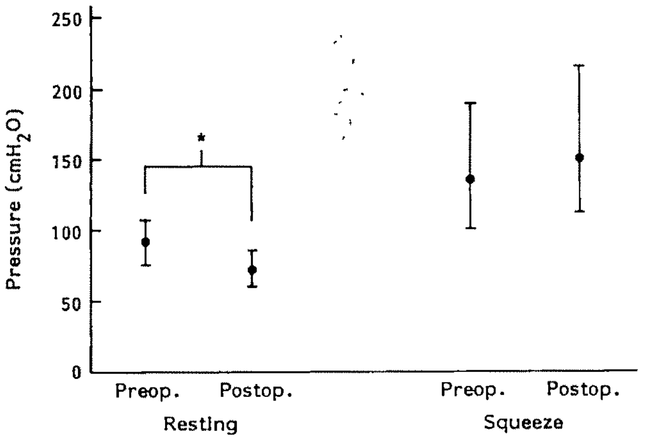

Figure 1 *Maximum resting anal pressure and squeeze pressure before and after restorative proctocolectomy by the eversion technique. Values are median (interquartile range). *P = 0·002 (Wilcoxon matched-pairs signed rank test)*

of the anal sphincter was 3·5 (2·5–4·5) cm before and 3·5 (2·0–4·5) cm after operation.

Sensation

Sensory thresholds before and after operation did not differ significantly in the upper, middle and lower anal canal (*Figure 3*).

Table 1 *Clinical outcome in 26 patients 3–21 months after restorative proctocolectomy by the technique of anorectal eversion*

Frequency of bowel action*	
Per 24 h	4·5 (3–9)
Night-time	0·5 (0–3)
Minor faecal leakage	1
Deferral of defaecation	
>30 min	23
>15 min	25
Discrimination of flatus from faeces and safe release of flatus	17

*Values are median (range)

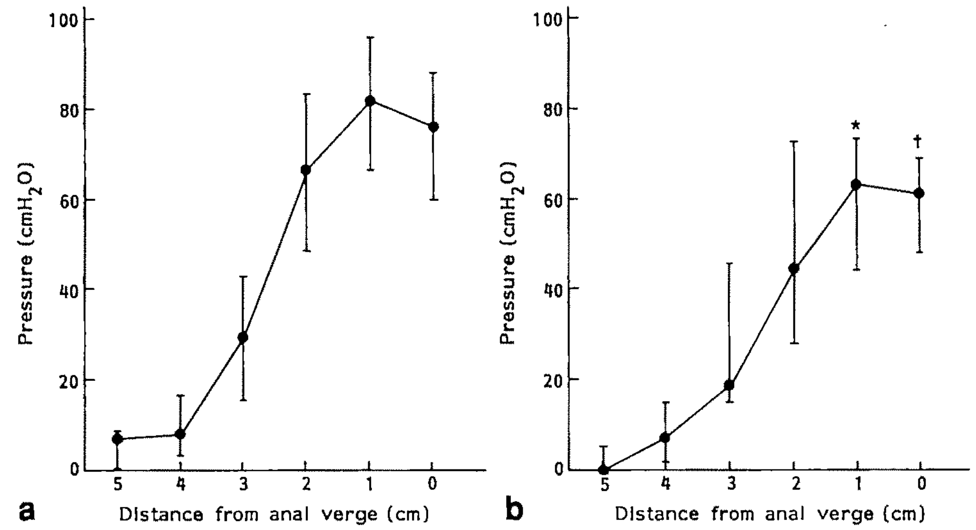

Figure 2 *Sphincter pressure profiles* **a** *before and* **b** *after restorative proctocolectomy by the eversion technique. Values are median (interquartile range). *P < 0·001; †P < 0·002* (versus *preoperative pressure, Wilcoxon matched-pairs signed rank test*)

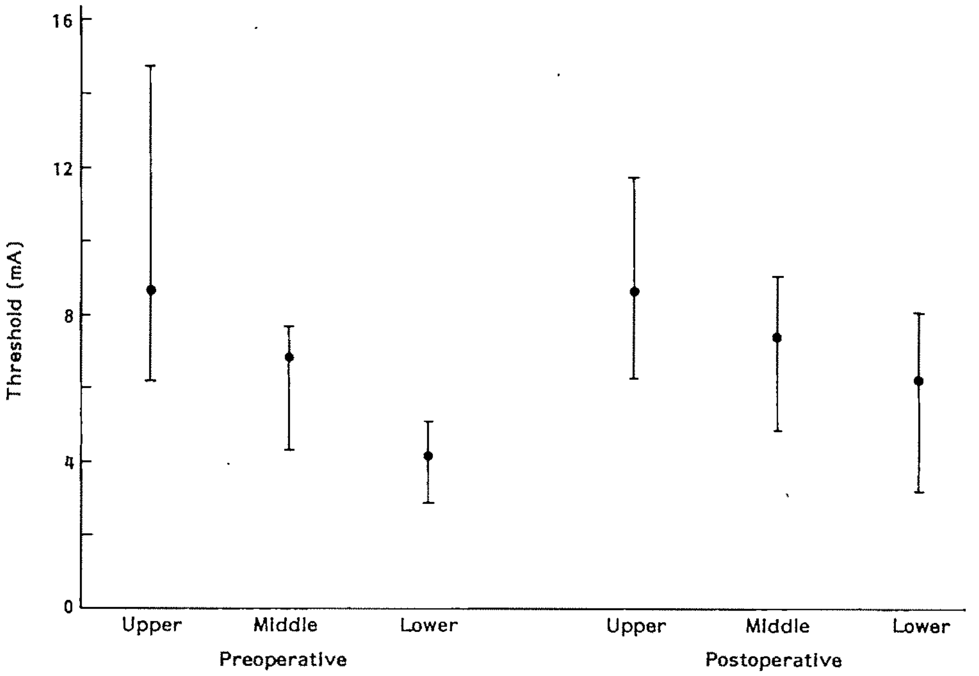

Figure 3 *Sensation in the anal canal measured by mucosal threshold electrosensitivity before and after restorative proctocolectomy by the eversion technique. Values are median (interquartile range). Differences are not significant*

Anorectal and pouch–anal inhibitory reflex

The reflex was found to be present in 26 patients before operation and in 23 afterwards.

Clinical results

These are shown in *Table 1*.

Discussion

The increasing popularity of the stapled end-to-end ileoanal anastomosis without mucosectomy has focused attention on the precise level at which the anastomosis should be constructed. The principal disadvantage of this procedure is that, if the ileoanal anastomosis is constructed too high above the dentate line, a cuff of inflamed rectal mucosa may remain, giving rise to local or systemic manifestations of colitis[11]. It is frequently difficult to obtain good access (especially in the obese male patient) to transect the anorectal sleeve at the correct level with the linear stapling device. In women, the ease of deep pelvic dissection and upward tenting of a mobile pelvic floor may result in the transection being made at too low a level and the upper part of the anal sphincter may be damaged or even excised.

One way to overcome the problems of 'blind' transection of the anorectal stump is to evert the stump through the anus. This manoeuvre has been used in the treatment of infants with Hirschsprung's disease[12] and has been advocated more recently in the surgical treatment of ulcerative colitis[3,4,13]. The anorectal eversion technique is still not widely used during restorative proctocolectomy because of its unfamiliarity to many surgeons and fears that the forcible traction often exerted on the anorectal stump might damage the sphincter. This may occur by direct trauma to its musculature and the adjacent pelvic floor or indirectly through damage to its nerve or blood supply.

All 26 patients in the present study were found before surgery to have normal anal pressure and sensation, and the rectoanal inhibitory reflex was noted to be present in each. Some 8 months after operation, resting anal pressure, although reduced, remained within the normal range in all patients; the resulting pressure profile was similar to that observed after end-to-end stapled anastomosis without the aid of anorectal eversion[1]. Maximum squeeze pressures were normal, anal sensation was undiminished, and a pouch–anal inhibitory reflex was present in 23 of the 26 patients.

The clinical outcome in the patients was satisfactory: all were continent, and their ability to defer defaecation and discriminate flatus from faeces was good. The function of the anal sphincter was found to be as good in this study as in previous reports of patients who had undergone end-to-end ileoanal anastomosis without anorectal eversion[14]. Both methods of constructing an end-to-end anastomosis, whether conventional or by eversion, are associated with a decrease in resting anal pressure. This is less than that following endoanal anastomosis and is not sufficient to cause significant impairment of function as judged by the clinical endpoints of faecal soiling, urgency of defaecation and discrimination between flatus and faeces.

Eversion of the rectum and anus during restorative proctocolectomy may cause minimal damage to the motor power of the anal sphincter, but overall function of the sphincter complex is not impaired.

References

1. Johnston D, Holdsworth PJ, Nasmyth DG *et al.* Preservation of the entire anal canal in conservative proctocolectomy for ulcerative colitis: a pilot study comparing end-to-end ileo-anal anastomosis without mucosal resection with mucosal proctectomy and endo-anal anastomosis. *Br J Surg* 1987; **74**: 940–4.
2. Holdsworth PJ, Johnston D. Anal sensation after restorative proctocolectomy for ulcerative colitis. *Br J Surg* 1988; **75**: 993–6.
3. Goligher JC. Eversion technique for distal proctectomy in ulcerative colitis: a preliminary report. *Br J Surg* 1984; **71**: 26–8.
4. Brough WA, Schofield PF. An improved technique of J pouch construction and ileo-anal anastomosis. *Br J Surg* 1989; **76**: 350–1.
5. Martin LW, Sayers HJ, Alexander F *et al.* Anal continence following Soave procedure: analysis of results in 100 patients. *Ann Surg* 1986; **203**: 525–30.
6. Nicholls RJ, Pezim ME. Restorative proctocolectomy with ileal reservoir for ulcerative colitis and familial adenomatous polyposis: a comparison of three reservoir designs. *Br J Surg* 1985; **72**: 470–4.
7. Utsunomiya J, Iwama T, Imajo M *et al.* Total colectomy, mucosal proctectomy and ileo-anal anastomosis. *Dis Colon Rectum* 1980; **23**: 459–66.
8. Roe AM, Bartolo DCC, Mortensen NJMcC. New method for assessment of anal sensation in various anorectal disorders. *Br J Surg* 1986; **73**: 310–12.
9. Keighley MRB, Henry MM, Bartolo DCC, Mortensen NJMcC. Anorectal physiology measurement: report of a working party. *Br J Surg* 1989; **76**: 356–7.
10. Cohen L, Holliday M. *Statistics for Social Scientists.* London: Harper and Row, 1982.
11. Martin LW, Torres AM, Fischer JE, Alexander F. The critical level for preservation of continence in the ileo-anal anastomosis. *J Pediatr Surg* 1985; **20**: 664–7.
12. Swenson O, Sherman JO, Fisher JH *et al.* The treatment and postoperative complications of congenital megacolon: a 25-year follow up. *Ann Surg* 1978; **182**: 266–73.
13. Telander RL, Perrault J. Colectomy with rectal mucosectomy and ileoanal anastomosis in young patients. *Arch Surg* 1981; **116**: 623–9.
14. Sagar PM, Holdsworth PJ, Johnston D. Correlation between laboratory findings and clinical outcome after restorative proctocolectomy: serial studies in 20 patients with end-to-end pouch–anal anastomosis. *Br J Surg* 1991; **78**: 67–70.

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SURGERY ABSTRACTS

Br. J. Surg. 1993, Vol. 80, January, 124–125

In November of last year we began an exchange of abstracts with the American journal Surgery. *This month sees the publication of summaries chosen from the November and December issues of that journal. A reciprocal selection of* BJS *abstracts appears in January's* Surgery. *Readers may be interested to note that the December issue of the American journal was given over to papers presented at the 13th Annual Meeting of the American Association of Endocrine Surgeons held in April 1992 in Miami, Florida.*

Surgery for malignant obstructive jaundice: Analysis of mortality

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Surgery on patients with malignant obstructive jaundice carries formidable morbidity and mortality rates. Clinical records of 120 consecutive patients who had serum total bilirubin levels of 100 μmol/L or greater before exploration were analyzed retrospectively to provide guidelines for better management. Although most patients underwent bilienteric bypass to either the extrahepatic (n = 45) or intrahepatic ductal system (n = 28), resection was possible in 32 (26.7%). Complications developed in 42 patients (35%), among whom 12 (10%) required reexploration and 32 (26.7%) died within the same hospitalization. Identification of risk factors associated with hospital deaths after surgery was conducted on 84 of the 120 (group A) patients randomly selected from the entire study period. Based on multivariate analysis, age greater than 65 years, a raised serum aspartate transaminase value greater than 90 IU, and serum urea level greater than 7 mmol/L before surgery were the risk factors selected from 39 different clinical (n = 6), laboratory (n = 26), and operative (n = 7) parameters studied. The predictive value was validated in the remaining 36 patients (group B), and a high-risk patient population had been isolated. Because both serum urea and aspartate transaminase values correlated significantly with the necessity of urgent exploration, aggressive nonoperative treatment should be used to control the emergency. Alternative therapeutic options or perioperative management should be considered for the selected high-risk patients before definitive surgical biliary decompression. (SURGERY 1992;112:891-6.)

Lymphatic and venous examination of the ulcerated leg: A preliminary report

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Background. *It has been widely accepted that deep venous thrombosis and venous incompetence initiate a series of events resulting in various ulcerations. The role of the lymphatic system in the progression of these events has not been extensively studied.*

Methods. *Twenty-three patients with nonarterial ulcerations of the legs were examined by phlebography and lymphangiography. All had recurrent ulcerations associated with nonpitting edema, brawny induration, and dermatitis characteristic of the postphlebitic syndrome. Arterial circulation was normal in all patients.*

Results. *Phlebographic abnormalities found were the presence of communicating vein incompetence in all 23 patients, varicose veins in six, and deep venous occlusion in one. Lymphatic abnormalities were also present in all patients. Extravasation in the area of the ulcer was seen in eight patients, dermal backflow in six, tortuosity and irregularity of the channels in four, and retention of contrast agent for more than 24 hours in seven.*

Conclusions. *Significant abnormalities of the lymphatic system exist in patients with leg ulcers caused by the postthrombotic syndrome. (SURGERY 1992;112:872-5.)*

P-glycoprotein expression and multidrug resistance in adrenocortical carcinoma

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Background. *The response of adrenocortical carcinoma (ACC) to adjuvant chemotherapy has been disappointing with no significant impact on survival. The normal adrenal cortex has very high levels of P-glycoprotein, an energy-dependent efflux pump of a variety of structurally unrelated chemotherapeutic agents. P-glycoprotein has been implicated as a cause of multidrug resistance in a variety of neoplasms. The purpose of this study was to evaluate P-glycoprotein expression in ACC.*

Methods. *Eleven patients with ACC had paraffin-embedded tumor evaluated for P-glycoprotein expression. These were analyzed by immunohistochemistry assay with a battery of four anti-P-glycoprotein antibodies (MRK-16, JSB-1, UIC-2, MDR).*

Results. *All eleven cases showed intense, predominantly membrane immunoreactivity for P-glycoprotein. In 10 of the cases, most tumor cells were immunoreactive with at least three antibodies, and six of 11 cases were positive for all four antibodies. In this small series no correlation existed between P-glycoprotein expression and tumor grade, stage of disease, or survival.*

Conclusions. *All 11 cases of ACC studied showed P-glycoprotein expression, which was similar to the normal adrenal cortex. This possible mechanism of multidrug resistance may help explain the significant chemoresistance seen in ACC. (Surgery 1992;112:981-6.)*

Granulocyte oxidative activity after thermal injury

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Background. *Alterations in granulocyte function after thermal injury have been described. We have serially studied the level of granulocyte cytosolic peroxidase activity in 23 thermally injured patients during the first 6 weeks after injury. The patients' mean age and burn size were 35.1 ± 15.7 years and $41.6\% \pm 16.8\%$ (range, 18% to 88%), respectively. Fourteen patients had concomitant inhalation injury, and the overall mortality rate was 4.3%.*
Methods. *Purified granulocytes were obtained from peripheral blood after red cell lysis and Ficoll-Hypaque (Pharmacia Inc., Piscataway, N.J.) gradient separation. Cells were loaded with dichlorofluorescin diacetate, and baseline fluorescence was measured by flow cytometry. After phorbol myristate acetate stimulation, fluorescence was measured again. Cells from unburned normal subjects were used as daily controls.*
Results. *The data are expressed as percent of stimulated control granulocyte fluorescence. Unstimulated patient granulocytes demonstrated a significantly higher baseline activity than did unstimulated controls (22.9% vs 15.4%; $p < 0.05$). Mean fluorescence from stimulated granulocytes was 114% of the control values ($p < 0.05$).*
Conclusions. *Granulocytes from thermally injured patients exhibited a baseline increase in cytosolic oxidase activity, suggesting in vivo activation and a greater than normal oxidase activity after in vitro stimulation. (Surgery 1992;112:860-5.)*

Relationships of parathyroid hormone, parathyroid secretory protein, parathyroid hormone messenger RNA, parathyroid secretory protein mRNA, and replication in human parathyroid adenoma and secondary hyperplasia tissues and cultures

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Background. *The purpose of this study was to clarify the relationships of extractable and secreted parathyroid hormone (PTH) and parathyroid secretory protein (PSP) in human parathyroid tumors to PTH messenger RNA (mRNA), PSP mRNA, and cell replication.*
Methods and Results. *In tissue cultures of seven adenomas and five secondary hyperplasias, we found a direct correlation for secreted PTH versus PSP for both adenomas and secondary hyperplasias. Secreted PTH:PSP was elevated for adenomas (11:1) compared to that of secondary hyperplasias (2:1), and adenomas secreted significantly more PTH and PSP than did secondary hyperplasias. In extracts of eight adenomas and six secondary hyperplasias, the ratio of PTH:PSP was unexpectedly low (2:1) and similar for both adenomas and secondary hyperplasias. The ratio of extractable PTH mRNA:PSP mRNA was extremely low for both adenomas (1:7) and for secondary hyperplasias (1:5). Flow cytometry indicated that percent replication was inversely correlated with PTH mRNA and PSP mRNA.*
Conclusions. *Increased PTH secretion by adenomas cannot be attributed to increased biosynthetic capacity because it is less than expected. Hypersecretion of PTH by adenomas and coincident marked reductions in PTH mRNA suggest either a defect in cytoplasmic storage of PTH or impairment of normal posttranslational degradation of PTH. As parathyroid tumor cells increase replication, PTH mRNA is reduced. Possible explanations for this include decreased PTH gene transcription or decreased mRNA half-life. (Surgery 1992; 112:1089-95.)*

Prospective study of the use of intraarterial secretin injection and portal venous sampling to localize duodenal gastrinomas

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Background. *Duodenal gastrinomas producing Zollinger-Ellison syndrome (ZES) are rarely imaged on preoperative studies. Measurement of serum gastrin levels by transhepatic portal venous sampling (PVS) or by sampling from hepatic veins after intraarterial secretin injection have been advocated as useful tests to identify these tumors before operation.*
Methods. *As part of a prospective study, selective intraarterial secretin injection has been performed in 36 consecutive patients with ZES, PVS has been performed in 30 of these patients, and the results have been compared.*
Results. *Gastrinomas were found at laparotomy in 33 of 36 patients (92%). Duodenal tumors were found in 18 patients (50%). The remaining patients had liver, pancreatic, or nodal disease (n = 15). Thirty-two of 36 patients (89%) had positive results with intraarterial secretin injection study, whereas 18 of 30 (60%) had a positive PVS gradient ($p = 0.02$, Fisher's exact test). The most common positive gradient with intraarterial secretin injection was found with injections of the gastroduodenal artery, and the most common positive gradient with PVS was found in the inferior pancreaticoduodenal (IPDV) or superior pancreaticoduodenal vein (SPDV). Fourteen of 18 (78%) patients with duodenal gastrinomas had a positive GDA injection, whereas five of 18 (28%) without duodenal tumors had a positive GDA injection ($p = 0.006$). Five of 16 patients with duodenal gastrinomas had a positive gradient in the IPDV or SPDV, whereas four of 14 without duodenal tumors had a positive gradient in the IPDV or SPDV (not significant).*
Conclusions. *Intraarterial secretin injection is more sensitive than PVS at localizing duodenal gastrinomas and should replace PVS in patients with ZES and occult tumors. (Surgery 1992;112:1002-9.)*

Correspondence

Laparoscopic splenectomy

Sir

We read with great interest the Surgical Workshop on laparoscopic splenectomy by Dr Delaitre and colleagues (*Br J Surg* 1992; **79**: 1334). We would like to report our experience of laparoscopic splenectomy involving a 62-year-old woman with idiopathic thrombocytopenic purpura failing to respond to steroids. She was pretreated with high-dose immunoglobulin (0·4 g/kg daily for 5 days), successfully raising the platelet count from 17×10^9/l to 238×10^9/l on the day of operation.

While the technique used was similar to that reported, we employed only four ports but, more importantly, felt that preoperative embolization of the splenic artery, as described by Dr M. Gazayerli of Troy, Michigan, USA (personal communication), was a sensible adjunct, particularly when the spleen is relatively enlarged. The advantages are that the spleen shrinks as a result of the embolization and the veins can be taken before the artery without worrying about congestion of the organ. Also, a degree of autotransfusion takes place and there is the added benefit of a little extra security as far as haemostasis is concerned when the vascular stapler is fired. Finally, the theoretical risk of arteriovenous fistulation should be reduced.

In our own case the spleen proved too large to place into a plastic bag and morcellate, but it was retrieved through a small 5-cm subumbilical incision without difficulty.

After operation the patient required only two doses of opiate analgesia. The operative time was 2·5 h with another hour for the preoperative embolization.

We do not agree that laparoscopic splenectomy should be confined to cases with haematological disease not associated with splenomegaly as, even if the spleen proves to be large and difficult to manipulate into a bag, a small transverse lower abdominal incision can be used for retrieval, thereby avoiding an upper abdominal incision and all its disadvantages.

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Managing swabs in the operating theatre: a new method

Sir

I read with interest the article by Mr McCombe and colleagues on managing swabs in the operating theatre (*Br J Surg* 1992; **79**: 776–7). It is refreshing to see a common sense approach to a practical problem in surgery.

I would commend the use of Curity sponge counting bags to the authors. These are manufactured by the Kendall company of the USA and each bag has five pockets. The pockets are partially divided by a small plastic weld. The weld allows the use of the bags to hold either ten small swabs or, having split the weld, five abdominal packs. Bags can be hung on a rack and swab numbers monitored constantly. The advantage of this bag over the single bag method is that each swab is separate in its own pocket and, if swab counts do not tally at the end of an operation, it removes the need to empty out and recount swabs from a single bag.

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Breast cancer in Nigerian women

Sir

The hospital-based survey on breast cancer from Nigeria by Mr Ihekwaba (*Br J Surg* 1992; **79**: 771–5) finds a low incidence of breast cancer and a high proportion of stage III disease when compared with reports from the West. The single most important factor for the low incidence is under-reporting of the disease, particularly in the older age groups. There is anecdotal evidence that many women do not seek hospital treatment for economic and/or sociocultural reasons. However, with increasing disease awareness, a rise in literacy and improving socioeconomic standards, there has been a significant increase in patients seeking medical advice in recent years. This is the likely cause for the marked increase in the numbers recorded in the second decade (1309) over the first 10 years (637) of the study. The overall frequency of 33·6 per 100 000 also shows a similar increase on the 13·8–15·3 per 100 000 previously reported from Africa[1–4].

It is of interest that the disease in Nigeria has the highest incidence in premenopausal women, in contrast to the situation seen in the West. It should therefore be regarded as a leading cause of death after maternal mortality in the younger woman. The lack of adequate resources for treatment mentioned in the paper was brought home to me during a trial of adjuvant chemotherapy for locally advanced breast cancer in premenopausal women conducted at the University Teaching Hospital in Maiduguri, Nigeria, a few years ago. Thirty-eight women (mean(s.d.) age 37·8(6·5) years) with tumours staged as $T_{3/4}N_{2/3}M_0$ underwent local surgical excision followed by cyclical chemotherapy using four agents (cyclophosphamide, methotrexate, 5-fluorouracil plus prednisolone). Fifteen patients completed the treatment and 12 remained recurrence-free during the first 3 years of follow-up. The majority (23 patients) opted out of the trial at various stages of treatment, largely because of patient non-compliance. As the vast majority of these women were from the lower socioeconomic strata, some form of financial assistance during their illness in addition to the provision of free medical care would have greatly reduced the default rate.

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1. Davies JNP, Wilson BA. Cancer in Kampala 1952–1953. *East Afr Med J* 1954; **31**: 395–416.
2. Hickey BB. Malignant epithelial tumours in the Sudanese. *Ann R Coll Surg Engl* 1959; **24**: 303–22.
3. Edington GM, Maclean CMU. Cancer rate survey in Ibadan 1960–1963. *Br J Cancer* 1965; **19**: 471–81.
4. Linsel CA. Cancer incidence in Kenya: 1957–63. *Br J Cancer* 1967; **21**: 466–73.

Ileal salvage from failed pouches

Sir

I should like to add a warning postscript to my Surgical Workshop concerning ileal salvage from resected pouches (*Br J Surg* 1988; **75**: 1227). Since then I have had to resect a further pouch in a 50-year-old man, and again reconstituted the terminal ileum with a continuous extramucosal monofilament closure of the 40-cm antimesenteric slit. This time there was serious leakage from partial breakdown requiring repair and a proximal defunctioning ileostomy. The stoma has since been closed, and the patient is well again and with a full complement of small intestinal tract.

In future, whereas I remain convinced of the propriety of ileal salvage, I would advocate a temporary proximal loop/spout ileostomy to defunction the involved loops (which terminate at the end stoma).

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Laparoscopic pyloroplasty for duodenal ulcer

Sir

The technique of truncal or selective vagotomy with gastric drainage by way of pyloroplasty in the treatment of duodenal ulcer is a well described and much performed operation. More recently, highly selective and truncal vagotomies have been performed laparoscopically[1] and, where necessary, the drainage procedure has been accomplished by laparoscopic pyloromyotomy, pyloroplasty or endoscopic balloon dilatation of the pylorus.

I have lately been involved in the management of a patient with duodenal ulcer that was refractory to medical management and required vagotomy and pyloroplasty because of scarring of the pylorus. While the laparoscopic vagotomy was unremarkable, the pyloroplasty was accomplished in a manner that was new to me and which made the construction of a pyloroplasty of Weinberg/Heineke–Mikulicz type extremely simple.

By raising the pylorus with the use of two Endo-Babcock (US Surgical, Norwalk, Connecticut, USA) clamps inserted through two 10-mm cannulas placed below the costal margins lateral to the rectus muscle on the opposite side of the abdomen, an Endo-GIA (US Surgical) stapling device inserted through a 12-mm cannula to the right of the midline midway between the xiphisternum and umbilicus could be manoeuvered over the tented-up pylorus and fired. This resulted in a haemostatic watertight pyloroplasty with no contamination of the peritoneal cavity. A gastroscope was manoeuvered through the pylorus beforehand to ensure that the posterior duodenal/stomach wall was not picked up by the Endo-Babcock clamp and to confirm adequate pyloroplasty. The patient experienced no complications, minimal postoperative pain and was feeding orally on the second day.

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1. Bailey RW, Flowers JL, Graham SM, Zucker KA. Combined laparoscopic cholecystectomy and selective vagotomy. *Surg Laparosc Endosc* 1991; **2**: 45–9.

Laparoscopic repair of perforated peptic ulcer

Sir

We were interested to read the Surgical Workshop by Mr Sunderland and colleagues (*Br J Surg* 1992; **79**: 785). Recently we too have used a laparoscopic surgical approach to patients with a presumed diagnosis of perforated peptic ulcer disease. However, there are differences between our approaches that merit discussion.

Patients with a diagnosis of perforated peptic ulcer, who would otherwise have been submitted to laparotomy, undergo laparoscopy following standard resuscitative measures. The patient is draped as for laparotomy. After pneumoperitoneum has been generated, the laparoscope is inserted through a 10-mm infraumbilical cannula. A washer–suction apparatus is passed through a 5-mm cannula placed in the mid-clavicular line midway between the umbilicus and right costal margin. The diagnosis is confirmed or refuted during a full diagnostic laparoscopy. If confirmed, the presence or absence of a naturally occurring omental patch is noted. If this is absent and the perforation is obviously gaping and exuding gastroduodenal contents, then we discontinue the laparoscopy and convert to a traditional open omental patch operation. If however, as is often the case, there is a naturally occurring omental plug, then we leave this alone and proceed to thorough peritoneal lavage using the washer–suction device via the 5-mm port. A volume of 2–3 litres warm saline is used for the lavage, obtaining a high flow rate by hanging the perfusate in a compression bag. Stab incisions are closed with subcuticular 3/0 Dexon (Davis and Geck, Gosport, UK).

We do not try to close the perforation laparoscopically. We believe the most important part of the omental patch operation, be it open or laparoscopic, is thorough peritoneal toilet. We see no merit in disturbing an omental patch already in place merely to spend a long time putting it back.

Laparoscopic suturing is time consuming, as testified by the report by Sunderland and colleagues. Patients with perforated peptic ulcer disease are often very ill and unsuitable for long surgical procedures. By the very nature of the condition, perforated ulcers tend to present out of hours and be operated on by surgeons in training. Not all trainees have laparoscopic suturing expertise, yet most are becoming familiar with diagnostic laparoscopy and would be able to perform a laparoscopic peritoneal lavage.

Like Sunderland and co-workers, we have as yet only small numbers of patients treated in this way and statistical analysis is thus meaningless. We have not had to reoperate on any patient treated by lavage alone. While the case is not yet proven by a prospective randomized trial, these patients appear to enjoy the advantages of reduced postoperative pain as well as the shorter postoperative recovery and hospital stay common to other abdominal laparoscopic techniques.

We believe our approach means that most patients can benefit from the advantages of a laparoscopic technique without having to undergo unduly prolonged general anaesthesia or requiring a surgeon with particular expertise in endoscopic suturing techniques.

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Total dysphagia from intramural haematoma following sclerotherapy for oesophageal varices

Sir

We read with interest the Case Report by Mr McGrath and colleagues (*Br J Surg* 1992; **79**: 781). This provided an excellent example of the potential risk of injecting toxic sclerosants into oesophageal varices or perivariceal tissue. Indeed, complications of endoscopic variceal sclerotherapy are reported to occur in up to 40 per cent of treatments and procedure-related deaths in 1–2 per cent of injection sessions[1–3]. On the other hand, therapy for variceal haemorrhage has been progressively directed away from portasystemic shunts, sclerotherapy being at least as good if not superior in terms of survival and preservation of hepatic function[4,5]. In addition, most studies show that sclerotherapy is superior to medical treatment when results are compared in terms of the immediate management of active bleeding and avoidance of recurrence[6–8]. However, in the face of the reported high rate of complications, an equally effective but safer endoscopic approach is urgently needed. This could be achieved by endoscopic rubber-band ligation, first introduced by Van Stiegmann *et al.*[9] in 1986. This technique is gaining wide popularity in the USA, being reliable, quick, easy and cheap. A prospective randomized trial comparing endoscopic sclerotherapy with ligation was recently reported[10]: although the two techniques proved equally effective in treating bleeding oesophageal varices, recurrent bleeding was less frequent in patients receiving endoscopic ligation than in those treated by sclerotherapy. Both mortality rates (28 *versus* 45 per cent) and complication rates (2 *versus* 22 per cent) were significantly lower in the ligation group. We therefore believe that endoscopic rubber-band ligation should be popularized in Europe as the first-choice option for treating bleeding oesophageal varices.

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1. Sarles HEJ, Sanowski RA, Talbert G. Course and complications of endoscopic variceal sclerotherapy: a prospective study of 50 patients. *Am J Gastroenterol* 1985; **80**: 595–9.
2. Schuman BM, Beckman JW, Tedesco FJ, Griffin JW Jr, Assad RT. Complications of endoscopic injection sclerotherapy: a review. *Am J Gastroenterol* 1987; **82**: 823–30.

3. Infante-Rivard C, Esnaola S, Villeneuve JP. Role of endoscopic variceal sclerotherapy in the long-term management of variceal bleeding: a meta-analysis. *Gastroenterology* 1989; **96**: 1087–92.
4. Warren WD, Henderson JM, Millikan WJ *et al.* Distal splenorenal shunt *versus* endoscopic sclerotherapy for long term management of variceal bleeding: preliminary report of a prospective, randomized trial. *Ann Surg* 1986; **203**: 454–62.
5. Spina GP, Santambrogio R, Opocher E *et al.* Distal splenorenal shunt *versus* endoscopic sclerotherapy in the prevention of variceal rebleeding: first stage of a randomized, controlled trial. *Ann Surg* 1990; **211**: 178–86.
6. The Copenhagen Esophageal Varices Sclerotherapy Project. Sclerotherapy after first variceal hemorrhage in cirrhosis: a randomized multicenter trial. *N Engl J Med* 1984; **311**: 1594–600.
7. Westaby D, MacDougall BR, Williams R. Improved survival following injection sclerotherapy for esophageal varices: final analysis of a controlled trial. *Hepatology* 1985; **5**: 827–30.
8. Westaby D, Hayes PC, Gimson AE, Polson RJ, Williams R. Controlled clinical trial of injection sclerotherapy for active variceal bleeding. *Hepatology* 1989; **9**: 274–7.
9. Van Stiegmann G, Cambre T, Sun JH. A new endoscopic elastic band ligating device. *Gastrointest Endosc* 1986; **32**: 230–3.
10. Van Stiegmann G, Goff JS, Michaletz-Onody PA *et al.* Endoscopic sclerotherapy as compared with endoscopic ligation for bleeding esophageal varices. *N Engl J Med* 1992; **326**: 1527–32.

Success rates for rehabilitation of vascular amputees: implications for preoperative assessment and amputation level

Sir

The paper by Mr Houghton and colleagues (*Br J Surg* 1992; **79**: 753–5) was an interesting and timely evaluation of the outcome of prosthetic rehabilitation of amputees. The report exemplified the difficulty in assessing the results of rehabilitation (in all areas of physical disability), which arises from a lack of common agreement on methods used to measure outcome. In amputee rehabilitation, the literature abounds with a profusion of scales that purport to quantify mobility or other facets of outcome. The mobility measurement scale adopted by the authors has the merit of brevity, but we would be interested to know what tests were applied to establish the validity of the scale e.g. sensitivity, repeatability, correlation with other scales.

It is stated that a score of 9 (maximum score 12) was accepted as indicating 'satisfactory' rehabilitation, leading to the conclusion that only 5 per cent of all patients were satisfactorily rehabilitated. To achieve this score, the amputee would have had to use the prosthesis to walk all waking hours, use the limb to walk indoors and outdoors without restriction and use no walking aid (not even one stick). Given the average age of vascular amputees and the likely coexistence of other disabling conditions, it could be said that the authors' adopted criterion for satisfactory rehabilitation is very demanding.

We would suggest that rehabilitation outcome should be measured in relation to the situation before amputation. For example, an outcome for an above-knee amputee of only walking indoors with an aid, modest in itself, would be considered a success if that same level of activity had been present before the onset of limb ischaemia limited by, say, arthritis, cardiorespiratory disease or stroke. On this basis we would regard a score as low as 4 as indicative of optimum rehabilitation for many of our patients. If mobility around the house equates to satisfactory rehabilitation, then well over 40 per cent of the authors' patients who were fitted with limbs achieved a good result.

Finally, restoration of gait is only one aspect of amputee rehabilitation and, as the paper shows, is irrelevant for half of all vascular amputees. Studies[1,2] have shown that psychological and social adaptation following amputation are independent of the level of amputation and degree of mobility achieved. Thus, those patients who are unable to make use of a prosthesis are not beyond rehabilitation in its broadest aspects.

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1. Goldberg RT. New trends in the rehabilitation of lower limb amputees. *Rehabil Lit* 1984; **45**: 2–11.
2. O'Toole DM, Goldberg RT, Ryan B. Functional change in vascular amputee patients: evaluation by Barthel index, PULSES profile and ESCROW scale. *Arch Phys Med Rehabil* 1985; **66**: 508–11.

Authors' reply

Sir

We thank Messrs Fyfe and Berridge for their interest in our paper and agree with their plea for a standard postoperative mobility scale for amputees. Having surveyed the literature extensively before writing our first paper[1], we feel our scale has much to recommend it. Other mobility scales are vague and ill defined, whereas that detailed in the paper is simple for the patient to complete and much more precise. The lack of precision in most other scales makes scientific comparison with ours almost impossible.

Messrs Fyfe and Berridge appear not to understand the scoring system. It is not the case that patients would have to use no walking aids at all and employ their prosthesis all the time to achieve a satisfactory mobility score of 9. Patients could still score 9 if they used their limb more than 50 per cent of waking hours, outside their home on occasions, had one stick as a support and did not feel unstable when walking on the flat, slopes and rough ground.

We agree totally that the assessment of the degree of mobility before amputation is ideal. So often, however, limb ischaemia develops gradually over a period of years, making this type of assessment difficult. What would perhaps be better would be a direct comparison of the rehabilitation of similar groups of patients who either have a successful arterial reconstruction or amputation. A preliminary study of 28 such patients in our unit, using two of the four questions from the same questionnaire, suggests a very much better functional outcome in the patients undergoing reconstruction. This finding would suggest that it is the amputation rather than the 'preamputation situation' that is limiting the patient. Further similar studies are badly needed.

We should like to emphasize that this paper was in no way intended as a criticism of the prosthetic services. It is rather an attempt to find out what happens to our amputees. As discussed in the paper, the outcome in our series of UK amputees is remarkably similar to the Swedish experience[2]. This fact suggests, as Messrs Fyfe and Berridge also emphasize, that more attention should be paid to other forms of rehabilitation apart from restoration of gait.

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1. Houghton A, Allen A, Luff R, McColl I. Rehabilitation after lower limb amputation: a comparative study of above-knee, through-knee and Gritti–Stokes amputations. *Br J Surg* 1989; **76**: 622–4.
2. Kald A, Carlsson R, Nilsson E. Major amputation in a defined population: incidence, mortality and results of treatment. *Br J Surg* 1989; **76**: 308–10.

Perforation of the bowel by suction drains

Letter 1

Sir

We read with great interest the Case Report by Messrs Reed, Wyman, Thomas and Zeiderman (*Br J Surg* 1992; 79: 679). We too have been interested in the potential impact of intraperitoneal drains. One possible explanation is the negative pressure exerted by the closed wound drainage vacuum devices.

An examination of the Reliavac (Davol, Cranston, Rhode Island, USA) closed wound drainage system commonly used intraperitoneally in the USA and developed primarily for closed wound drainage following axillary, inguinal or breast resection, showed that the pressure generated reaches −180 mmHg. For less powerful closed wound drainage systems such as the Jackson–Pratt (Baxter, Deerfield, Illinois, USA), the pressure generated is under −60 mmHg, which at least in theory would be less likely to cause complications. It was also noted that the practice of 'stripping' of silicone surgical drains will further increase the pressure by an additional −80 mmHg.

These observations have led us to abandon high-pressure intra-abdominal drainage systems and decrease our overall use of closed drainage in elective abdominal procedures. We agree with Mr Reed and colleagues that drains, particularly in this country, are almost certainly overutilized. The evidence to support their use in this age of intra-abdominal collections readily identifiable by computed tomography and the drainage of such collections, either percutaneously or by limited open drainage, would argue for controlled studies to see whether intra-abdominal drains have any useful role. Sadly, the endpoint is somewhat difficult to determine.

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Letter 2

Sir

I read with interest the Case Report by Mr Reed and colleagues (*Br J Surg* 1992; 79: 679). I suspect that the authors' suggestion that bowel perforation by suction drains is under-reported is correct. I have also had experience of three cases of bowel perforation by suction drains.

The first patient was a 32-year-old man who had undergone elective small bowel resection for Crohn's disease. A further laparotomy was performed for peritonitis, and multiple perforations were found in the small bowel adherent to the suction drain. The patient made a full recovery but had a longer hospital stay than would have been expected for the primary procedure.

The second patient was a 50-year-old man who had undergone emergency total gastrectomy for haemorrhage from extensive peptic ulceration. A second laparotomy was performed for peritonitis, and several small perforations were found adjacent to the suction drain in the oesophagus and jejunum. The patient died from persisting sepsis.

The third patient was a 35-year-old man who had undergone colonic resection for ulcerative colitis. A second laparotomy was performed for peritonitis at which multiple small bowel perforations were found, consistent with damage secondary to suction drainage. The patient made a full recovery but again the hospital stay was lengthened by the need for a secondary procedure.

Although all of these cases provide only anecdotal evidence for the dangers of suction drains in abdominal surgery, it is my practice to use a Robinson's type of non-suction drain in the abdominal cavity and reserve the usage of suction drains for the drainage of the perineum, breast and subcutaneous tissues and in extra-abdominal vascular procedures.

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Meconium ileus: a review 1972–1990

Sir

Epidemiological studies frequently provide valuable insight into the pathogenesis of diseases. A paper appearing recently in the Journal attests to the high prevalence of meconium ileus caused by cystic fibrosis in a Caucasian population: 53 confirmed cases presented to a surgical unit from 1972 to 1990 (*Br J Surg* 1992; 79: 571–3). Your readers might be interested to note that meconium ileus is by no means a rarity in localities like ours, where cystic fibrosis is virtually unknown. During the past 10 years we have seen eight cases of simple meconium ileus and six of complicated meconium ileus in the form of volvulus (two), atresia (two) and meconium peritonitis (two). All infants presented with intestinal obstruction soon after birth. Two neonates were promptly relieved of obstruction after a barium enema confirming the diagnosis and the passing of copious amounts of lumpy meconium. The remainder came to laparotomy. Surprisingly enough, the findings were identical to those of classical meconium ileus associated with mucoviscidosis. In three patients there were characteristic pellets of grey mucus, while the rest had only tenacious viscid meconium without pellet formation. The operative procedures included Roux-en-Y ileostomy in five patients, double enterostomy in three and primary anastomosis in four. There was no operative death. Two babies developed recurrent meconium obstruction despite complete evacuation at operation. They responded well to repeated irrigation with acetylcysteine solution via the ileostomy. One baby suffered recurrent episodes of rectal prolapse, complicated later by rectal stricture which was treated successfully by dilatation. All children have enjoyed normal growth, even though two girls continue to pass beads of faeces resembling rabbit's stools, requring prolonged administration of acetylcysteine.

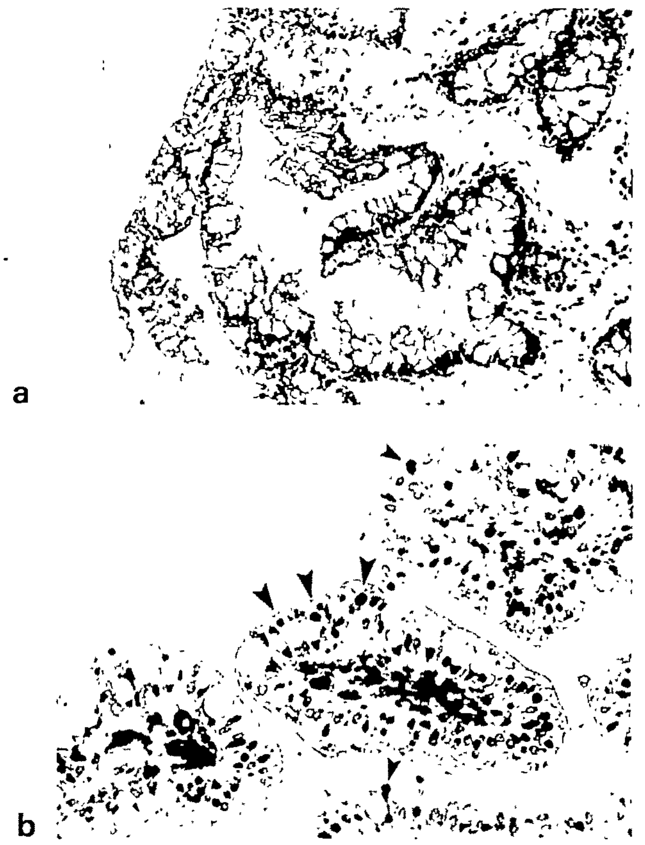

Figure 1 *Sections of ileum demonstrating* **a** *an excessive number of goblet cells and distended mucus glands in patients characterized by mucus pellets and* **b** *numerous deeply eosinophilic globules (arrows) within epithelial cells in patients with only tenacious meconium. (Haematoxylin and eosin stain, original magnification in* **a** *×200 and in* **b** *×400)*

Rectal biopsy confirmed Hirschsprung's disease in one patient from each group. Sweat tests were uniformly negative. Pancreatic biopsies in two cases were reported as normal. With the distinct exception of those from the two neonates with Hirschsprung's disease, the majority of bowel specimens showed the typical histological appearance of prominent goblet cells and distended mucus glands. In addition, in those patients with mucus pellets, the goblet cells were so numerous that they formed a continuous layer. In the two patients with only sticky meconium, abundant eosinophilic globules were seen inside most of the epithelial cells (*Figure 1*). They were more deeply stained than the extracellular mucoprotein. It appears that abnormal secretion from small intestinal mucus glands plays the main role in the causation of inspissated meconium.

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Vascular inflow exclusion and hepatic resection

Sir

I read with interest the article on vascular inflow exclusion and hepatic resection by Dr Taniguchi and colleagues (*Br J Surg* 1992; **79**: 672–5). I agree with their conclusion that vascular inflow exclusion may not be essential for successful hepatic resection, but it is not fully supported by the data they present.

First, they put various resection cases in group 1 that are actually partial hepatic resections without vascular exclusion or standard lobectomies. Of 32 patients in the group, there are five cases of hepatectomy involving less than one segment and 14 of lobectomy. Major lobectomy should not be included in the same group as the other partial hepatic resections, particularly involving less than two segments. Standard major lobectomy is performed similarly to hepatic resection with vascular exclusion in the sense of treating the vessels supplying the hepatic lobe.

Second, I cannot find the tumour diameter or tumour location in each group. Even if hepatectomy is performed without vascular exclusion, small tumours can be resected without much bleeding when situated in the lower part of segment V or VI or segments II or III.

Third, cirrhosis and non-cirrhosis should not be mixed up in a group: their intrahepatic vascular pattern is quite different, as shown on hepatic angiograms, and cirrhotic livers are usually associated with coagulation disorders that may increase intraoperative bleeding.

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Authors' reply

Sir

We acknowledge Dr Ezaki's comments on our paper. First, we would like to define the term hepatic resection, since there may have been some confusion. In our paper a right lobectomy refers to a right trisegmentectomy, a left lobectomy to a lateral segmentectomy, and a hepatectomy to a right or left bisegmentectomy[1,2].

In a hepatectomy, hepatic dissection after division of both the portal vein and the hepatic artery on the operative side is never standard[1,3]. When a right lobectomy is carried out after division of these vessels, the dissecting line is along the part of the liver with a blood supply. Even if a right or left hepatectomy is carried out, bleeding can occur from the raw surface on the opposite side of the liver. If inflow exclusion is performed during hepatectomy after division of these vessels, the case should be classified within the total inflow exclusion group (group 3) when a comparison of liver remnant function is made. When checking postoperative liver function, cases of right or left hepatectomy without vascular inflow exclusion must be included in group 1 (no hilar vascular exclusion).

We disagree with Dr Ezaki's second comment. We think that operative blood loss is not related to tumour size, but to the volume of liver resected. That is, even if a tumour is small, a wide resection may produce massive bleeding. Accordingly, we reported the extent of resection in *Table 2*. No tumorectomy was carried out in the current study. Tumour site may affect operative blood loss. For example, a tumour near the major hepatic vein may result in massive bleeding. However, we think there is no difference in blood loss according to the liver segment removed. The resection of segments other than II, III, V or VI may produce massive bleeding (as he pointed out) if the incision is inappropriate because only an abdominal approach is possible. However, using a thoracolaparotomy[4] resection of segment VII or VIII can be performed as easily as resection of the other liver segments.

It may be true that coagulation disorders are associated with liver cirrhosis[5], but the influence of this condition on operative blood loss is unclear. The current study showed no significant differences between patients with and without liver cirrhosis in group 1, 2 or 3. Indeed, blood loss in patients with liver cirrhosis was less than in those without cirrhosis in group 2. Moreover, the correlation coefficient between 15-min indocyanine green clearance rate ($ICGR_{15}$) and blood loss was very small, showing the relation to be insignificant. Accordingly, cirrhotic and non-cirrhotic cases were combined, and the number and $ICGR_{15}$ value were listed in *Table 1*. Because of so-called negative data, there is actually no difference when there is no significant difference statistically.

The point of our paper is that a successful operation can be carried out if bleeders on the raw surface are treated without vascular inflow exclusion. From our experience, there is no more bleeding from the raw surface of a cirrhotic liver than from the raw surface of a non-cirrhotic organ. Bleeding is associated with hepatic hilar treatment of the cirrhotic liver. Accordingly, we think that our results can be applied to both cirrhotic and non-cirrhotic livers.

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1. Schwartz SI. Hepatic resection. *Ann Surg* 1990; **211**: 1–8.
2. Blumgart LH. Liver resection – liver and biliary tumors. In: Blumgart LH, ed. *Surgery of the Liver and Biliary Tract.* New York: Churchill Livingstone, 1988: 1252.
3. Huguet C, Gavelli A, Chieco A *et al.* Liver ischemia for hepatic resection: where is the limit? *Surgery* 1992; **111**: 251–9.
4. Lortat-Jacob JL. Hepatectomie roite reglée. *Press Med* 1952; **60**: 549–51.
5. Oguro A, Taniguchi H, Daidoh T *et al.* Factors relating to coagulation, fibrinolysis and hepatic damage after liver resection. *HPB Surg* (in press).

Primary *versus* staged resection for acute obstructing colorectal carcinoma

Sir

I read with interest the recent article by Dr Sjödahl and co-workers (*Br J Surg* 1992; **79**: 685–8). Their concluding comment, that resection of a rectosigmoid tumour with colocolic anastomosis is possible in most instances, may have some merit but is not in any way supported by the figures produced.

As they suggest, primary resection of obstructing right colonic tumours is not controversial. But of the cases presented there were only 18 resections of left-sided lesions, and 11 of these were Hartmann's procedures, leaving only seven patients receiving resection and anastomosis as advocated. In view of the shortage of cases, it is particularly surprising that they chose to exclude patients in whom barium could be forced proximal to the obstruction. They do not cite any evidence to suggest that such patients are a separate group with a different prognosis to others with clinical and plain radiological evidence of obstruction. Because of valve-like effects in the bowel, failure to demonstrate retrograde flow may not imply complete antegrade obstruction or vice versa. It is possible that such findings reflect more the patient's ability to retain the enema and the radiologist's skill and persistence than severity of disease.

The length of stay and morbidity and mortality rates for restoring bowel continuity after Hartmann's procedure were included, but no mention was made of how many patients had reconstructive operations after Hartmann's procedure. From other series, one would expect this to be considerably less than 100 per cent.

Good results for emergency colorectal resection by specialist surgeons in busy centres are to be applauded. However, most surgeons, whether or not trainees of 5 or more years' standing, have more sporadic opportunities to operate on such patients and should not be seduced into underestimating the difficulty of performing a good cancer resection and a reliable anastomosis in the presence of distended fragile and unprepared bowel. There is still a place for preliminary decompression of left-sided colonic obstruction with subsequent resection of uncompromised bowel in preference to a brave attempt at resection frequently resulting in an effectively permanent colostomy following Hartmann's procedure.

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Authors' reply

Sir

Mr Hinson's concern that the issue about resection and primary anastomosis for obstructing colonic cancer is moving too quickly is much appreciated. As he writes, the obstruction may be more or less complete, and the real problem is with tumours of the rectosigmoid colon. As clearly seen from our paper, where a rigorous definition of obstruction was used, there will be only a minority of patients with such tumours who are suitable for resection with primary anastomosis. The majority of patients have either more proximal tumours suitable for primary anastomosis or more advanced tumours that may not be resectable.

We believe there are several points to be made. The tumour should always be explored and resection attempted by a surgeon who is competent for such procedures. Once the tumour has been resected, the choice between primary anastomosis or Hartmann's procedure may depend on the experience of the surgeon. The colorectal surgeon then has the advantage of greater experience. The only statistical difference we found about the management and outcome of obstructing tumours was that experienced surgeons performed better in the above aims. We certainly agree that adequate tumour resection can be difficult, but the point is to match the patients' needs with surgical competence. It is equally important to prepare the patient adequately for operation and to find the best surgeon for the job, or preferably two surgeons who can share the difficulties.

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Early gastric cancer

Sir

We read with great interest the retrospective analysis by Dr Farley and colleagues (*Br J Surg* 1992; **79**: 529–42) on treatment results of early gastric cancer. The survival rate in their series (68 per cent at 5 years) is far less than those of series from Japan reporting figures of 90–95 per cent. Interestingly, their survival was equivalent to that of an age- and sex-matched control group.

However, one has to note that only 32 of the 48 patients underwent oesophagogastroduodenoscopy to define the extent of disease; multicentric early gastric cancer, which can be present in up to 13 per cent of cases[1], might therefore not have been detected. Furthermore, nothing is reported on the margins of safety when performing local excision or subtotal gastrectomy, the number of patients who had their lymph nodes dissected, the number of nodes removed, or the number of nodes examined by the pathologist. Therefore, it might be assumed that some of these tumours treated were node-positive lesions, or were incompletely resected.

These figures should by no means be taken as standard for Western countries, and this assumption is reinforced by data presented at the recent American Society of Clinical Oncology meeting[2]. The survey on gastric cancer surgery in the USA presented by Wanebo *et al.* reports survival rates of 65 per cent after 5 years and 53 per cent after 7 years for stage I disease. The authors state that neither the operation nor the pathological examination is sufficiently standardized to draw conclusions or to ensure that this type of cancer is adequately treated.

Since October 1981, 812 patients with gastric cancer were treated at our department. Of these, 364 (44·8 per cent) underwent standard gastrectomy (R_2 compartment removal, including splenectomy, clearing of the lymph node stations 1–12, and removal of the pancreatic capsule). Of those, 245 patients were judged to have undergone resection for cure (R_0) and their operative mortality rate was 3·4 per cent. Early gastric cancer was present in 85 of the patients (10·5 per cent) and their median age was 61·3 years. Survival at 5 years in this group of patients was 87·4 per cent including postoperative deaths[3]. Similar data were reported recently from two Italian groups[4,5].

Two facts have to be discussed. (1) Why, in Dr Farley's report, is the 5-year survival of a group of patients treated for gastric cancer with curative intent not better than that in the control group? One would expect tumour-related death in the treatment group to be minimized. (2) The type of operation reported by Dr Farley and colleagues differs widely. It cannot be ruled out that incomplete resections were performed leaving behind lymph nodes or gastric wall occupied by tumour.

From our point of view the approach to early gastric cancer should not be different from that used in the more advanced stages. Our data show that even in Western countries 5-year survival rates >85 per cent result from routine radical gastrectomy with lymphadenectomy. Furthermore, efforts to treat patients with gastric cancer at an early stage of disease should encourage the extensive use of endoscopy.

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1. Noguchi Y, Ohta H, Takagi K *et al.* Synchronous multiple early carcinoma of the stomach. *World J Surg* 1985; **9**: 786–93.
2. Wanebo HJ, Kennedy BJ, Chimmel J, Winchester D, Steele G. Survey of patterns of care for gastric cancer in the United States. *Proceedings, American Society of Clinical Oncology*. San Diego, California, May 1992.
3. Schlag P, Buhl K, Schwarz V, Möller P, Herfarth Ch. Die neue TNM-Klassifizierung und ihre Auswirkung auf die chirurgische Behandlung des Magenkarzinoms. *Chirurg* 1989; **60**: 8–15.
4. Pacelli F, Bellantone R, Doglietto G *et al.* Extensive *versus* limited lymph node dissection for carcinoma of the stomach: a 10-year experience. *Br J Surg* 1992; **79**: S49 (Abstract).
5. Guadagni S, Ibi I, Gola P *et al.* Ten-year follow-up of 159 patients with early gastric cancer. *Br J Surg* 1992; **79**: S49 (Abstract).

Authors' reply

Sir

We appreciate the comments of Drs Hohenberger and Buhl regarding our paper. Because the study period started in 1965, upper gastrointestinal endoscopy was not employed in all patients, although it has recently become standard practice. Most patients underwent subtotal gastrectomy or a more radical resection, the only exceptions being two elderly patients with limited disease who had local excision of their tumours. Margins of 5 cm were obtained when possible, eleven patients had an extended lymph node dissection (R_2) and the mean number of lymph nodes examined pathologically was 8·7 and 11·0 for subtotal and radical subtotal gastrectomy respectively.

The authors are to be congratulated on their personal results with early gastric cancer, but their median patient age was nearly a decade less than in our population (69 years). This, or the increased heartiness of the European patient, may explain the differences in 5-year survival.

In response to their two questions, we would not expect patients with early gastric cancer to have a better survival than the general population, any more than we would predict a survival advantage for patients with advanced gastric cancer. While most tumour resections were less radical than many recent Japanese and European authors have advocated, only two known intra-abdominal recurrences (4 per cent of patients) occurred. We still contend that advanced patient age, rather than any treatment factor, resulted in our seemingly decreased patient survival results. Furthermore, the lack of impact on patient outcome compared with a control population implies that the treatment had no significant adverse effect in this study group.

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Book reviews

An Atlas of Clinical Syndromes – A Visual Aid to Diagnosis. 2nd ed.

H.-R. Wiedermann, J. Kunze and H. Dibbern. 266 × 197 mm. Pp. 564. Illustrated. 1992. London: Wolfe.

Our previous edition of this book is much thumbed through regular use on the paediatric surgical neonatal intensive care unit, and this new edition is an expansion and improvement. It demonstrates 204 clinical syndromes that 'can be identified by an experienced observer with a physician's eye alone, and do not require extensive laboratory investigation'. There are black-and-white photographs of varying quality and radiographs when relevant; colour plates have been deliberately excluded and I accept the wisdom of that decision. For those keen to read the original description of eponymous syndromes, there are plenty of secondary references, but only occasionally the primary reference itself. The indices are very comprehensive so you can find the relevant syndrome from several different directions – name, major finding, or organ abnormality. Although the rapid expansion of clinical genetic units has made the clinical diagnosis in babies and children with dysmorphic features much less dependent on the paediatrician or paediatric surgeon looking after them, there is enormous pleasure in identifying a syndrome before having it confirmed by the geneticist. I look forward to converting this shiny new book into a much-thumbed version too.

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Atlas of Organ Transplantation

T. E. Starzl, R. Shapiro and R. I. Simmons. 310 × 255 mm. Pp. 342. Illustrated. 1992. New York: Gower Medical. US $150.

Those of us who love comics (and I count myself among the masses) may be expecting something akin from a book with this title, and from that point of view this volume is a partial disappointment. I was expecting a series of illustrations and diagrams that could be followed from picture to picture, giving the practical details of the techniques of organ retrieval and transplantation. Indeed, the book is lavishly illustrated in colour with numerous excellent clear diagrams and superb photographs. However, in true Pittsburgh style, the authors have tried to 'do it all' in this single volume, covering the entire breadth of transplantation and the illustrations do not have legends but are only quoted in the text. Included is a detailed chapter on transplantation immunology and an excellent chapter on vascular access surgery. The chapters on transplantation of the various organs include details of patient selection, preoperative and postoperative care, immunosuppression and management of complications. As expected, the chapter on liver transplantation is particularly authoritative. There are also enjoyable chapters on transplantation of skin, bone, cornea and bone marrow. There is some repetition and inconsistency, as each chapter has been written by different authors, with little cross-reference. There are also omissions, for example the duct occlusion method of pancreatic transplantation (which is still used successfully in some centres) was not mentioned in the appropriate chapter, and I was surprised that the chapter on multiorgan transplantation (which the Pittsburgh team pioneered) was not more detailed. I suspect the authors have been ill advised to dispense with legends, which would have made the book easier to read and to reference. However, it is an impressive text that gives a necessarily didactic but practical lesson in the full breadth of organ transplantation; many surgeons (not least the hundreds of visitors to the Pittsburgh programme) will find it essential reading.

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Tutorials in Clinical Surgery in General. Vol. 1

F. G. Smiddy. 215 × 137 mm. Pp. 311. Not illustrated. 1991. Edinburgh: Churchill Livingstone. £19·95.

The recent changes in the structure of the Fellowship examination of The Royal College of Surgeons of England have necessitated some revision of the relevant textbooks. This text is by the same author as the well known '*Tutorials in Surgery 1* and *2*', who has managed to produce a compact book that will be of benefit to many in their preparation for the new examination. It is well laid out, concise, easily readable, and interspersed with interesting and relevant historical anecdotes. The book deals with a wide variety of topics with emphasis on the practice and principles of surgery, and the pathophysiology of trauma and surgical disease. The author is a member of the Court of Examiners of The Royal College of Surgeons of England and the contents of the book are designed around the College's guide to the Fellowship. Because of the nature and size of the book, it does not cover in any great detail the traditional general surgical topics, but it should have wide appeal beyond the confines of a readership wishing to prepare for the new examination.

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The Ageing Surgical Patient: Anaesthetic, Operative and Medical Management

D. L. Crosby, G. A. D. Rees and D. G. Seymar (eds). 236 × 150 mm. Pp. 457. Illustrated. 1992. Chichester: John Wiley. £65.

Anaesthetists and surgeons have been made aware through the many recent morbidity and mortality studies of the need to define the risks of all surgical operations and then, if appropriate, to optimize the patient's preoperative treatment. In the elderly patient, the incidence of concurrent pathology is high. As the number of patients aged 65 years or over accounts for about 20 per cent of all hospital admissions, there is real likelihood of important pathophysiological changes being present in many surgical patients. The value of rehydration, preoperative physiotherapy, drug prophylaxis against sepsis and postoperative thromboembolism are well recognized, and present techniques discussed. The need for a book like this has never been greater. The reviewer must ask, therefore, how well the authors have addressed the task of identifying the various pathological and pharmacological challenges. What tests are really relevant in our assessment of the fitness of these patients and what anaesthetic approaches can be offered?

The combination of editors (a surgeon, an anaesthetist and a specialist in geriatric medicine) have clearly achieved their aims. The opening chapter describes the general principles of the physiology and pathophysiology of ageing and then progresses to outline the important anaesthetic considerations in the elderly. My only criticism is the rather scant discussion of the various methods available for postoperative analgesia in these at-risk patients. This may reflect the present lack of good controlled clinical trials addressing these issues in the elderly (too much opiate may result in respiratory depression and postoperative oxygen desaturation; too little analgesia may limit the efficacy of respiratory physiotherapy, with the development of atelectasis and infection). Studies are needed to assess the relative efficacy of intramuscular systemic opioids, patient-controlled analgesia and epidural analgesia in various groups.

The individual systems of the body and their associated surgical problems are well reviewed in the remaining chapters. My favourites were those by Gingell and Dodds (the urological patient) and Chant and colleagues (vascular surgery), but this is not to decry the value of the others.

Despite having adequately assessed the patient and provided ideal anaesthesia, postoperative care may require the facilities of an intensive care unit. Mortality rates in such units are higher in these elderly patients. However, as stated clearly by Foy (Chapter 12), 'age must not be used as a cut-off point to refuse admission for intensive care treatment'. It is essential that both medical and nursing staff regularly review the progress of these elderly patients, so that decisions to pursue or withhold active treatment are made on a rational basis.

At the end of the book is a chapter by John Lunn that should be read by *all* surgeons and anaesthetists. What are the risks of anaesthesia and surgery in a particular patient? Are we really doing the correct thing by operating on near-moribund elderly patients? If there are no high-dependency or intensive care beds, are we justified in submitting elderly patients to prolonged surgery from which they may succumb in the immediate postoperative period? Outcome is measured not only by mortality rate, but also by quality of life.

This book offers answers to many of the questions I have raised. I hope the messages are widely disseminated to anaesthetists and surgeons, both junior and senior.

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Terminology, Definitions and Diagnostic Criteria in Digestive Endoscopy. 2nd ed.

Z. Maratka (ed.). 245 × 168 mm. Pp. 141. Illustrated. 1988. Bad Homburg: Normed Verlag. DM49.

Illustrated Terminology, Definitions and Diagnostic Criteria in Digestive Endoscopy

Z. Maratka (ed.). 245 × 168 mm. Pp. 64. Illustrated. 1992. Bad Homburg: Normed Verlag. DM69.

These companion volumes stem from the work of the Committee of the World Society of Digestive Endoscopy (OMED), which was established in 1978. The purpose was to provide a strict terminology of endoscopic and laparoscopic findings that would provide a uniform international language. Each descriptive term is accompanied by a code that permits computerization. The first English edition of the *Terminology* was published in 1984 and was subsequently followed by editions in five other languages. A 2nd updated edition appeared in 1988, followed by an *Illustrated Terminology* in 1992 providing 156 endoscopic views of the normal and abnormal gastrointestinal tract.

While the principle of the venture is admirable, the outcome is in some ways disappointing. Terms such as 'fundus' of the stomach, 'angiodysplasia' and 'proctitis/colitis' must be avoided in favour of 'fornix', 'angiectasia' and 'red (hyperemic)'. Instead of 'erosive oesophagitis' we must use 'hemorrhagic esophagopathy'. The extensive use of American-style English spellings is most uncomfortable to those accustomed to the Oxford English Dictionary; the literal translation of some central European terms results in a disconcerting pseudo-English – 'red bleeding *per rectum*' becomes 'hematochezia (enterorrhagia)'. The codes seem overly elaborate: for 'spasm' it is '1.1.3.1.2' and for 'melena' '1.6.4.2.3'. A 'yellowish' liver at laparoscopy is to be coded '7.3.6.3.2.2'. At times the whole exercise becomes almost unreal. A regular dilated pancreatic duct is coded '8.1.2.1.1.3.2.1' – why not simply give the diameter? There is an index but this is not user friendly.

Endoscopists in training will find the *Illustrated Terminology* useful to browse through. Each of the 156 pictures is accompanied by a helpful line drawing, although the accompanying codes are a distraction. (Incidentally, Barrett's oesophagus is illustrated but under the title of 'brachyesophagus'.) There are no laparoscopic pictures.

Recommendation: inspect before you buy.

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Medical Management of the Surgical Patient

G. J. Merli and H. H. Weitz (eds). 209 × 125 mm. Pp. 462. Not illustrated. 1992. London: W. B. Saunders. £19·50.

This book sets out to provide an up-to-date guide to medical management of the surgical patient. It is ambitiously aimed at a wide readership: anaesthetists, surgeons, physicians, physicians in training and medical students. There are 19 chapters by 27 authors dealing with diseases involving most systems of the body. The authors are all American and there are some recommendations for investigations that are clearly coloured by the medicolegal problems besetting medicine in the USA. It is particularly unfortunate that the first chapter deals with medical consultation in an unnecessarily involved and didactic fashion. Read on, however, because most of the other chapters are excellent. Generally the topics are covered in a comprehensive fashion and it is pleasing to see that the value of history taking and physical examination are given proper emphasis in the assessment of the preoperative patient. The chapters on outpatient anaesthesia and malignant disease are extremely banal and could have been omitted. In a few instances the emphasis is wrong; for example, the section on endocrine disorders devotes twice as much space to thyroid disease as to diabetes, and the views expressed on the perioperative management of diabetes could be challenged.

Despite these minor problems, the book is comprehensive, well referenced and the management strategies well argued and presented. It can be thoroughly recommended for all medical personnel involved in the care of surgical patients. The valuable appendices provide a quick aide memoire to the problems associated with major surgical procedures in a format that is easy to access. This section should be particularly helpful to doctors in training.

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Advances in Surgery. Vol. 84

F. G. Moody, W. Montorsi and M. Montorsi (eds). 240 × 165 mm. Pp. 465. Not illustrated. 1992. New York: Raven Press. US $137·50.

This book is Volume 84 in a long line of symposia publications in the past decade from Raven Press. It is the outcome of a symposium on advances in surgery held in Milan in 1990. There are 96 chapters, covering aspects of the whole spectrum of surgery and surgical science from transplantation to microsurgery of the hand, from ophthalmology to proctology.

Most contributions are the reflections and opinions of the moderators of the individual sessions – usually one Italian contributor and one surgeon from the international panel of visitors. Some contributions, e.g. on cancer of the oesophagus, represent a substantial review of the papers presented, while others seem to reflect the expert opinion of the moderator. Most are light reading and contain many interesting gems of information for the non-specialist in the field.

The intended readership of the book is difficult to define. General surgeons will find the subject matter too diffuse and of insufficient depth in their area of interest. For the same reason it will be of limited value to the Fellowship candidate. Nevertheless, if picked up in the library it is a most interesting book to browse through.

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Notices and announcements

21 January 1993
London Vascular Debating Group Symposium–Vascular Trauma
London, UK
Information: Mr J. H. N. Wolfe, St Mary's Hospital, Praed Street, London W2 1NY, UK

11–12 February 1993
British Surgical Stapling Group Fourth Annual Symposium
Birmingham, UK
Information: Sally Smith, BSSG, c/o King's Ride Park, King's Ride, Ascot SL5 8BP, UK

22–24 February 1993
Sixth Annual Congress of the North American Society of Phlebology on the Advances in Sclerotherapy and the Advances in Surgical and Medical Treatment of Venous Disease
Lake Buena Vista, Florida, USA
Information: North American Society of Phlebology, 511 Encinitas Boulevard, Suite 111, Encinitas, CA 92024, USA

5–7 March 1993
Impact of HIV Infection on the Gastrointestinal Tract
Bologna, Italy
Information: Noema Congressi, Via Lame 24, 40122 Bologna, Italy

12–15 March 1993
7th Congress of the Western Pacific Association of Critical Care Medicine
Hong Kong
Information: Ms E. Lindsay, Secretariat, International Conference Consultants Ltd, Suite A/B, 16 F, Casey Building, 38 Lok Ku Road, Sheung Wan, Hong Kong

19–20 March 1993
2nd European Congress on Ambulatory Surgery
Brussels, Belgium
Information: Dr Cl. De Lathouwer, Brussels One Day Clinic, Nouvelle Clinique de la Basilique, 37–47 Rue Pangaert, B-1080 Brussels, Belgium

29–30 March 1993
General Thoracic Surgery: Surgery of the Esophagus
Boston, Massachusetts, USA
Information: Department of Continuing Education, Harvard Medical School, PO Box 825, Boston, Massachusetts 02 117, USA

31 March–2 April 1993
UICC Kyoto International Symposium on Recent Advances in Management of Digestive Cancers
Kyoto, Japan
Information: Professor T. Takahashi, Department of Surgery, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602, Japan

5 April 1993
Injury Research Group 1993 Meeting
Milton Keynes, UK
Information: Dr R. N. Barton, North-western Injury Research Centre, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

14–16 April 1993
Association of Surgeons of Great Britain and Ireland Annual Meeting
Birmingham, UK
Information: Caroline Ross, Association of Surgeons of Great Britain and Ireland, at The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

18–22 April 1993
International Congress on Advances in Brain Revascularization
Eilat, Israel
Information: Orta Ltd, 2 Kaufman Street, PO Box 50 432, Tel-Aviv, Israel 61 500

19–22 May 1993
Eighty-fourth Annual Meeting of the American Association for Cancer Research
Orlando, Florida, USA
Information: AACR Office, Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, Pennsylvania, USA

3–5 June 1993
First European Congress of the European Association for Endoscopic Surgery
Cologne, Germany
Information: Medikon-Heide Harzheim, Irmtraud Surmann, PO Box 50 14 70, D-5000 Köln, Germany

7–8 June 1993
8th International Symposium – Applied Physiology in Clinical Respiratory Care
Rotterdam, The Netherlands
Information: Dr O. Prakash, Thorax Centre BD 164, Dijkzigt Hospital, Dr. Molewaterplein 40, 3015 Rotterdam, The Netherlands

8–11 June 1993
World Association of HPB Surgery 1st European Congress of Surgery
Paris, France
Information· EHPBS Congress Secretariat, Congress House, 65 West Drive, Cheam, Surrey SM2 7NB, UK

9–12 June 1993
The Endocrine Society 75th Annual Meeting
Las Vegas, Nevada, USA
Information: Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

4–9 July 1993
Endosurgery – the State of the Art
Hamilton Island, North Queensland, Australia
Information: Kathy Noble, Centre for the Study of Endosurgery, Department of Surgery, Alfred Hospital, Commercial Road, Prahran, Victoria 3181, Australia

5–8 July 1993
First International and Eighth European Conference on Clinical Hemorheology
Vienna, Austria
Information: Professor E. Ernst, Department of Physical and Medical Rehabilitation, University of Vienna, AKH Währinger Gürtel 18–20, 1097 Vienna, Austria

6 July 1993
Current Issues in Epidemiology: the Prevention and Control of Chronic Disease
Cambridge, UK
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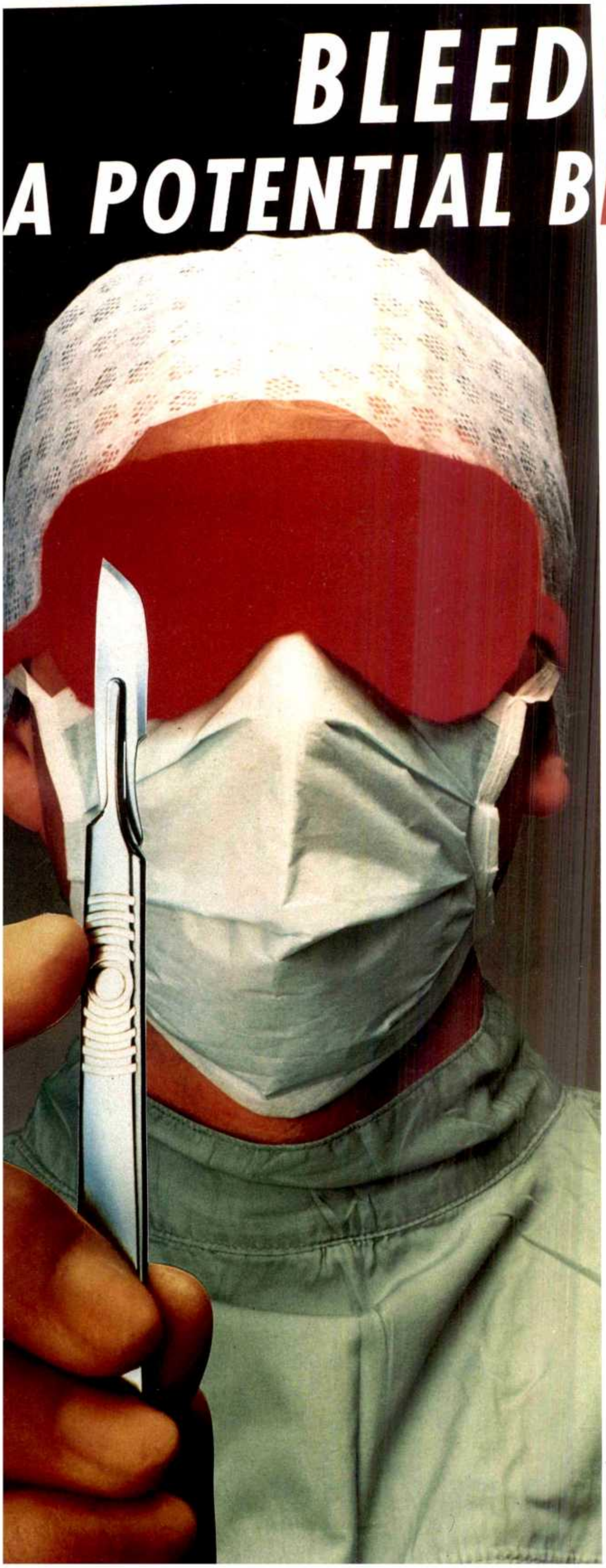

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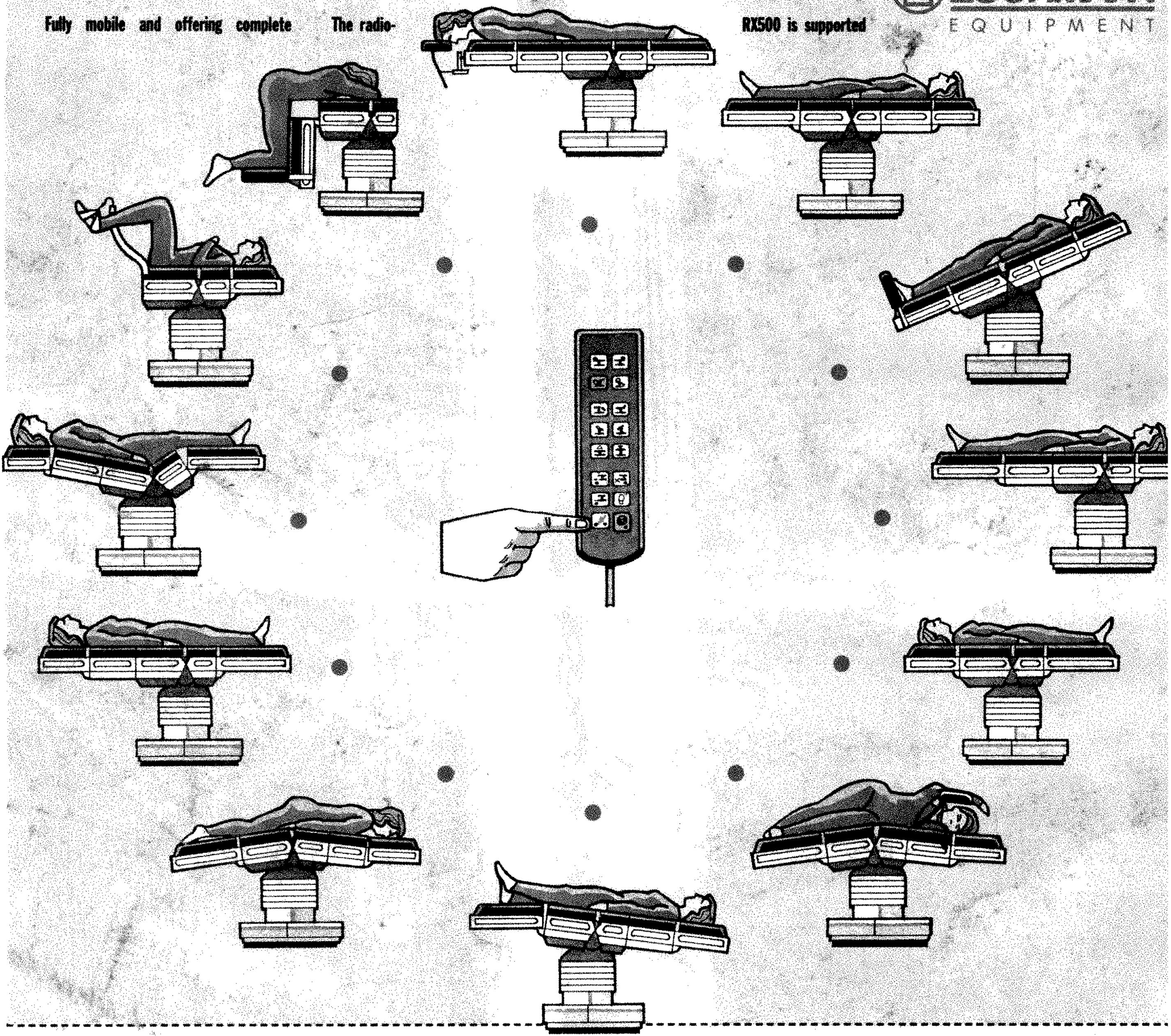

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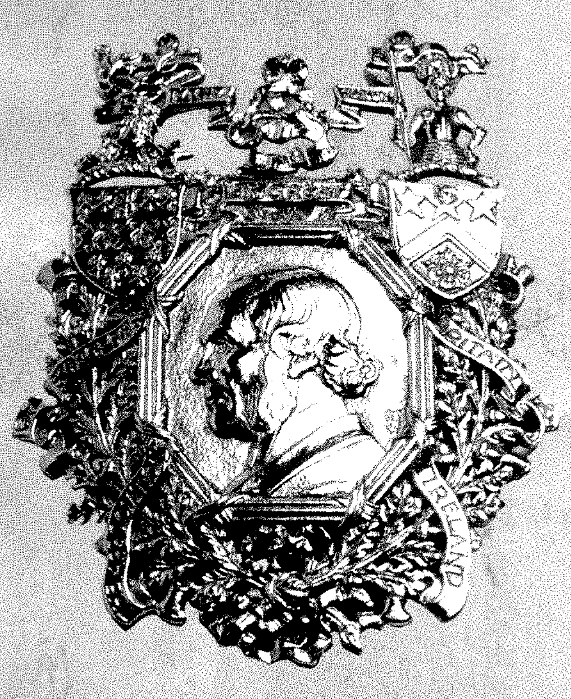

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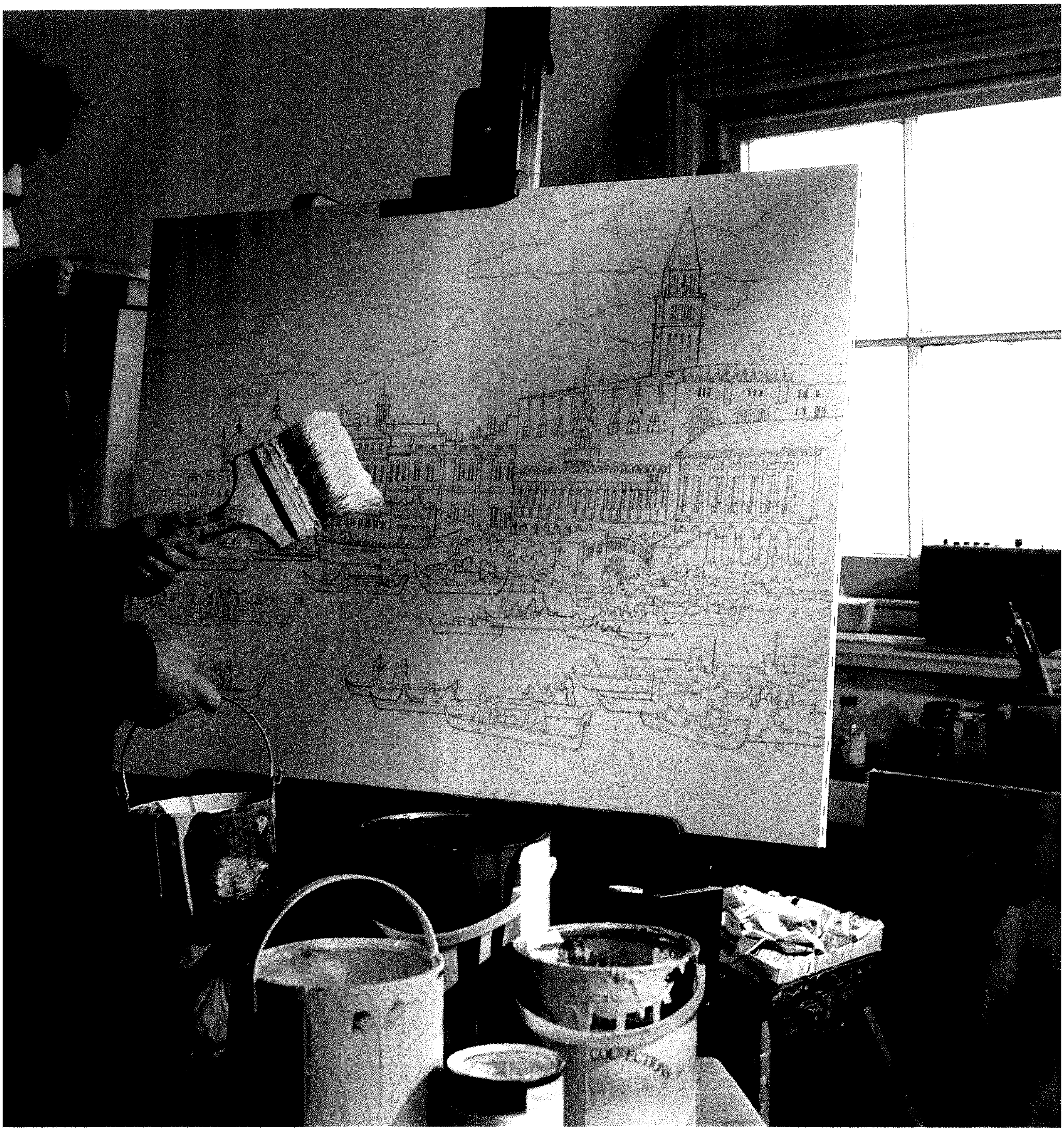

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PANCREATIC
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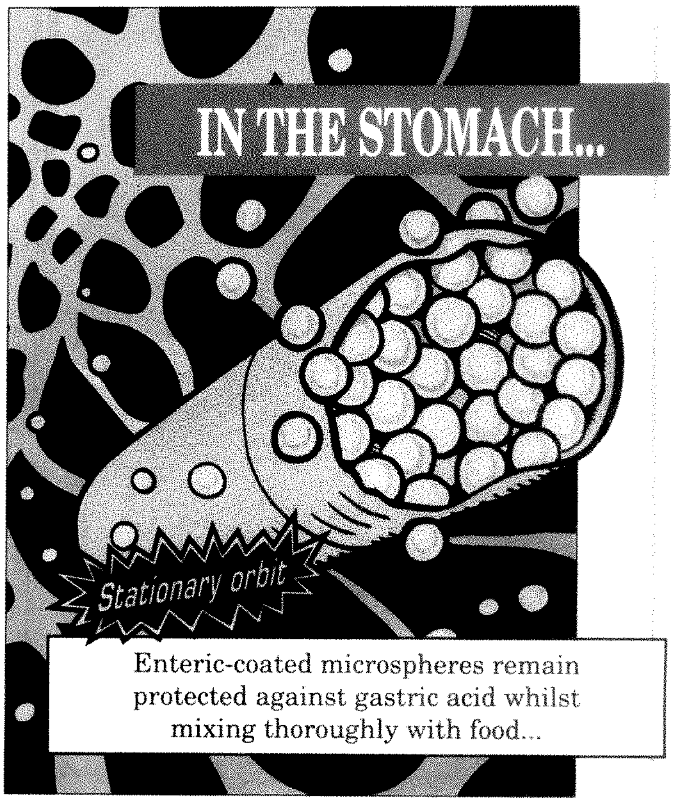
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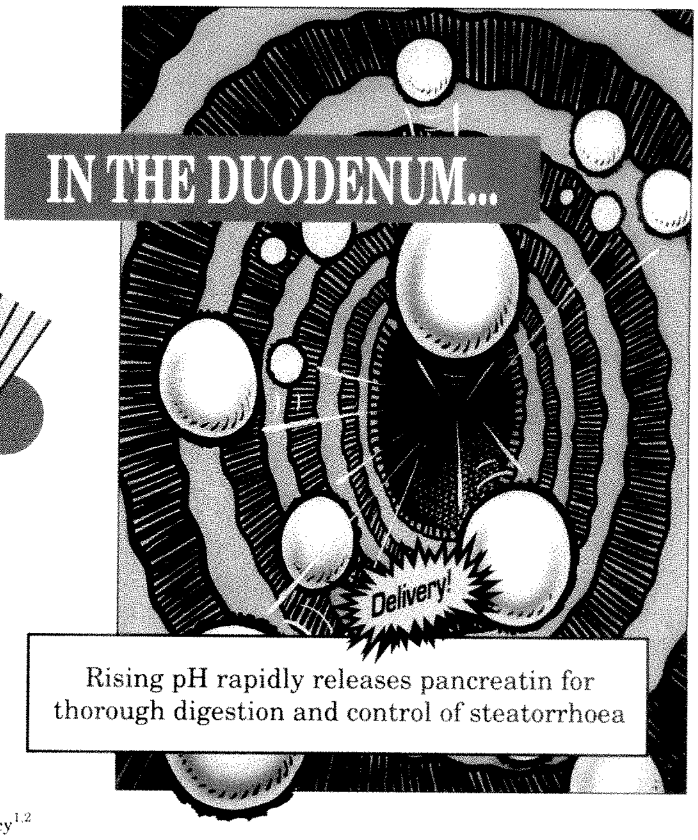
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References
1. Stead R J et al. *Thorax* 1987; **42**: 533-37
2. Beverley D W et al. *Arch Dis Child* 1987; **62**: 564-68

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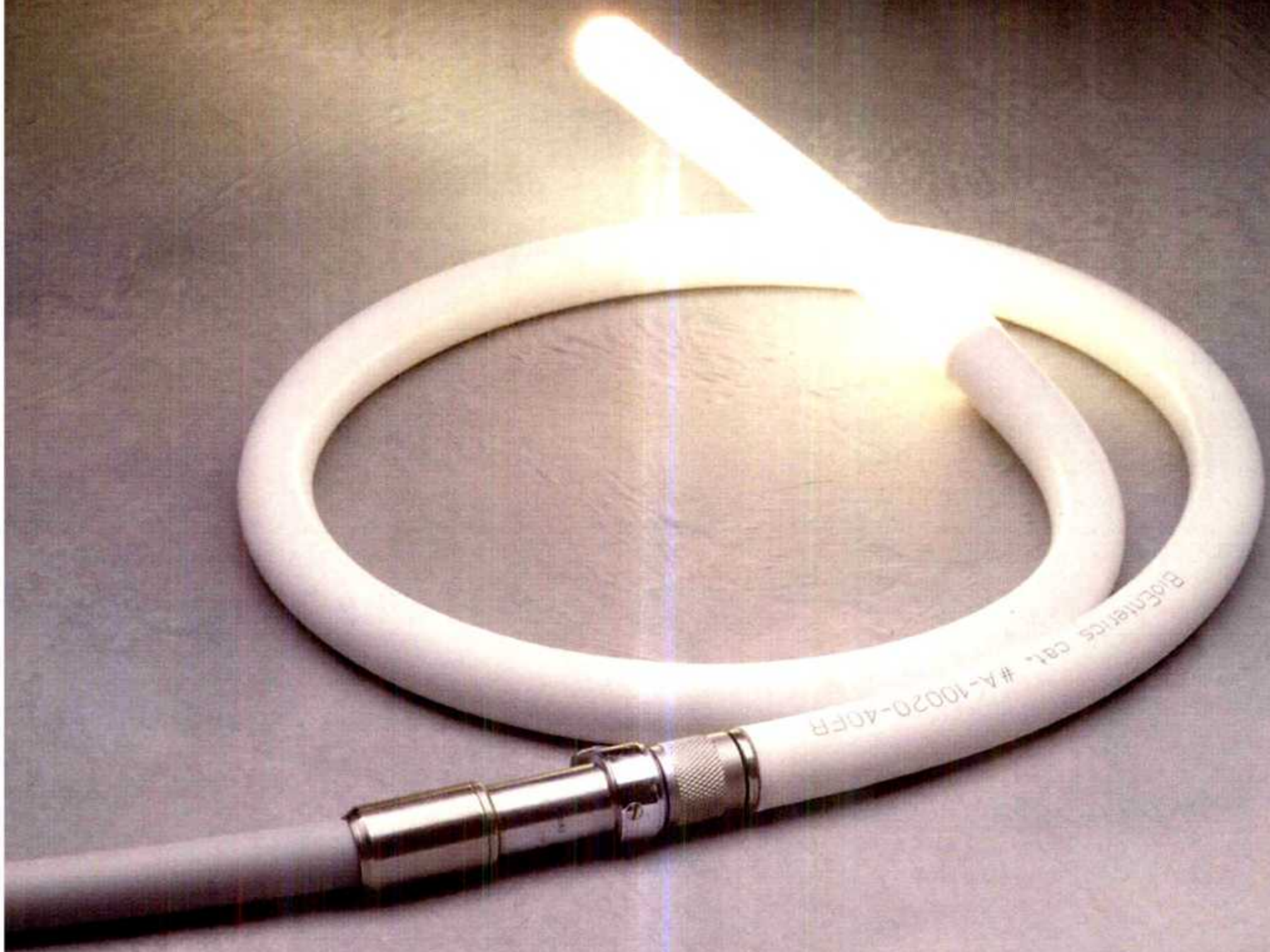

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Further sketches of Members from the British Isles.

PROFESSOR DOUGLAS MILLER

James Douglas Miller (born 1937) has been Professor of Surgical Neurology at Edinburgh since 1981, and before that held a similar appointment in Virginia, USA (from 1975). His early training had been in Glasgow, where he qualified as a doctor. He has served on the Neurosciences Board of the Medical Research Council (1984–1988). He has recently been elected a Fellow of The Royal Society of Edinburgh and President of the Society of British Neurological Surgeons.

MR MICHAEL PIETRONI

Michael Cyril Pietroni (born 1937) is a consultant surgeon at Whipps Cross Hospital, London, where for several years he acted as organizer for the renowned Final FRCS Course. Appropriately, he has been both a member of the Examinations Committee and Secretary of the Court of Examiners at The Royal College of Surgeons of England. He was President of the Surgical Section of The Royal Society of Medicine in 1990. His clinical interests are centred on vascular and oesophageal surgery.

PROFESSOR JOHN FITZPATRICK

John M. Fitzpatrick (born 1948) is Professor of Surgery at University College, Dublin, and the Mater Misericordiae Hospital. He trained in surgery and urology in Dublin and London and was a senior lecturer at Trinity College Dublin (1981–1986) before taking up his present appointment. Within urology his interests lie particularly in ureteric motility and obstruction, and in renal blood flow. He is a past President of the Urological Research Society.

Robin Williamson

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Br. J. Surg. 1993, Vol. 80, February, 138–140

Monocyte expression of class II antigens

It is always difficult to define scientific originality, but Almroth Wright has been given much of the blame and so deserves at least some credit for the present wave of enthusiasm for stimulation of host defences against microbial infection. It is interesting to speculate what ultimate effect his views, prejudices and insights may have had on his pupil Alexander Fleming in recognizing the antimicrobial properties of penicillin. Our fascination with antibiotics has lasted nearly 50 years and it is only in the past decade that investigative momentum has redeveloped in the broad area of stimulation of a variety of innate host defence mechanisms.

Antibiotics have unquestionably played a profound role in the modernization of medicine. One has only to look at the virtual disappearance in developed countries of the poststreptococcal illnesses of glomerulonephritis and rheumatic cardiac valvular disease to appreciate what the use of antibiotics has accomplished. On the other hand, it has become increasingly clear that even skilful rotation and an ever broadening spectrum of antimicrobial agents do not always fully prevent or cure infection, even that caused by susceptible organisms. Antibiotics continue to play a major role in patient care and are uniquely effective in providing systemic prophylaxis for operative or incisional infection. However, patients who are gravely ill with abnormalities of overall metabolism, nutrition or bodily function, or are seriously injured, frequently die as a result of infection despite the regular, judicious and even sequential use of antibiotics to which the offending organisms are sensitive. This realization is not new and a few surgeons have meticulously studied some components of the host defence process[1].

Our laboratory undertook an inquiry some 7 years ago into the components of the host defence processes, fully convinced that no measurable parameter would be predictive of clinical outcome. It was believed then that the extent of measurable abnormalities would be insignificant and unpredictive of clinical infection; indeed, the plan of the experiment was simply to study sequentially as many host defence parameters as possible. We expected to find that these were all unassociated with outcome in badly injured trauma patients known clinically to be likely to develop serious infection and that none was in any way predictive, or even characteristic, of patients who developed infection compared with those who did not[2]. To our surprise, empirical observations regarding monocyte expression of class II histocompatibility antigens (human leucocyte antigen (HLA)-DR) emerged as a statistically significant characterization of severe infection. The focal point of this essay is to affirm that this evolutionarily early physiological function is truly important and predictive. Present observations are now based on the original 20 patients plus an additional 41 similar cases[3]. The importance of monocyte HLA-DR antigen expression has also been shown in a randomized prospective comparison of a specific therapy in a multicentre trauma trial[4].

With thousands of observations made on hundreds of patients, we cannot yet fully define to what extent these abnormalities of monocyte function are intrinsic or constitutive characteristics, and to what extent they represent an exaggerated response to injury[5]. These observations have been made over 7 years in two different laboratories with different technical personnel and, in the most recently completed studies, from four different medical centres across the USA. The data from the initial 61 patients indicated the important correlative role of monocyte class II antigen expression in the process of infection. The levels of expression in patients who were destined to avoid serious or invasive infection rapidly returned to normal within 1 week of injury; levels of monocyte antigen expression in those who developed fatal or non-fatal infection either did not return to normal or did so only after the third or fourth week following injury, at which time the infection was often resolved. Furthermore, in the multicentre prospective trial a single early determination of the level of monocyte class II antigen expression was predictive of outcome with respect to both death and infection. Monocyte HLA-DR antigen expression, when added to an age-adjusted Injury Severity Score and a simple scheme of degree of bacterial

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contamination for the injury, was again predictive of outcome in the interferon (IFN) γ trial[4].

We have attempted to define normality with respect to monocyte HLA-DR antigen expression[5]. Our best interpretation is that in 10–15 per cent of a presumed normal population a relatively low percentage of monocytes express the HLA-DR antigen. Other individuals, whom we presume to be marginally normal, are disposed to subnormal HLA-DR antigen expression because of severe injury, shock and resuscitation. We therefore postulate that, for a small number of patients who are injured, such injury takes place in the presence of a constitutive abnormality. Other patients seem to express an acquired abnormality of monocyte antigen expression that possibly reflects a less than healthy response to shock, injury, resuscitation and surgical treatment. It may be important that restoration of this abnormal response occurs promptly.

If monocytes from patients who have either low percentage expression and/or relatively low mean fluorescent intensity (low density of HLA-DR antigen expression) are incubated in the presence of certain substances, values often return towards normal. Not surprisingly these substances include 'immunostimulants' such as lipopolysaccharide, muramyl dipeptide, IFN-γ and monophosphoryl lipid A. IFN-γ is illustrative of several points, in that incubation of monocytes without any stimulants has been shown to return the proportion of monocytes that express HLA-DR towards normal, but incubation in the presence of IFN-γ was required to restore fully normal values. This latter observation was confirmed by *in vivo* studies during the multicentre trauma trial[4]. Throughout the course of the 10-day period of therapy, patients who received IFN-γ had monocyte HLA-DR antigen expressions that were in the nearly normal range; expression was well above the range for those being treated with placebo. On withdrawing IFN-γ on the tenth day after injury, the values precipitously declined to the same level of activity that characterized monocytes from placebo-treated individuals. These test substances have numerous physiological actions other than restoration of monocyte class II antigen expression[6], but it may well be that their effect on monocytes is the most important of their corrective functions. Chaudry *et al.*[7] indicated, in a valid murine clinical model of haemorrhagic shock, that monocyte antigen presentation is a critical parameter that is returned to normal levels with IFN-γ therapy. Furthermore, they correlated return to normal values with increased survival in the experimental setting.

In this issue, Professor Guillou and colleagues at St Mary's Hospital, London, provide an important parallel to studies of patients undergoing trauma[8]. Their work confirms these concepts in a high-risk elective surgical population, providing the preoperative data that have been missing from our studies. The similarities with work previously reported are a further indication that class II antigen expression is an important predictor as well as a likely therapeutic target.

The purpose of this report is less to argue the relative primacy of monocytic antigen expression than to demonstrate that it plays a key early role, perhaps with numerous other substances, in the host defence response. An observation, perhaps of the greatest significance, is that monocytes from trauma patients receiving IFN-γ therapy were amenable to further *in vitro* improvement of HLA-DR antigen expression by incubation in the presence of lipopolysaccharide. Clearly, sequential reconstitution or stimulation is a valid concept[9,10], and it appears that monocyte expression of HLA-DR antigens may be an important indicator of the effectiveness of future therapies. Dosage and timing will be critical in further analyses; the first is obvious, but optimum sequence and timing with respect to multiple agents will be difficult to unravel.

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1. Alexander JW, Dionigi R, Meakins JL. Periodic variation in the antibacterial function of human neutrophils and its relationship to sepsis. *Ann Surg* 1971; **173**: 206–13.
2. Polk HC Jr, George CD, Wellhausen SR *et al.* A systemic study of host defense processes in badly injured patients. *Ann Surg* 1986; **204**: 282–99.
3. Hershman MJ, Cheadle WG, Wellhausen SR, Davidson PR, Polk HC Jr. Monocyte HLA-DR antigen expression characterizes clinical outcome in the trauma patient. *Br J Surg* 1990; **77**: 204–7.
4. Polk HC Jr, Cheadle WG, Livingston DH *et al.* A randomized prospective clinical trial to determine the efficacy of interferon-γ in severely injured patients. *Am J Surg* 1992;

163: 191–6.

5. Cheadle WG, Hershman MJ, Wellhausen SR, Polk HC Jr. HLA-DR antigen expression on peripheral blood monocytes correlates with surgical infection. *Am J Surg* 1991; **161**: 639–45.
6. Livingston DH, Malangoni MA. Interferon-gamma restores immune competence after hemorrhagic shock. *J Surg Res* 1988; **45**: 37–43.
7. Chaudry S, Ayala A, Ertel W, Stephen RW. Hemorrhage and resuscitation: immunological aspects. *Am J Physiol* 1990; **259**: R663–78.
8. Wakefield CH, Carey PD, Foulds S, Monson JRT, Guillou PJ. Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery. *Br J Surg* 1993; **80**: 205–9.
9. Grbic JT, Mannick JA, Gough DB, Rodrick ML. The role of prostaglandin E_2 in immune suppression following injury. *Ann Surg* 1991; **214**: 253–63.
10. Faist E, Markewitz A, Fuchs D *et al.* Immunomodulatory therapy with thymopentin and indomethacin: successful restoration of interleukin-2 synthesis in patients undergoing major surgery. *Ann Surg* 1991; **214**: 264–75.

Announcement

Eurochirurgie/Eurosurgery '93

Following the successful Second European Congress of Surgery in Brussels in June 1992, the Journal is pleased to continue its association with Eurochirurgie. Our plans include publication of the abstracts from Eurosurgery '93 as a supplement to the September issue of the Journal. All oral presentations and selected posters will be included in the abstract book of the meeting. This will be distributed free to all regular subscribers of the Journal.

Once again, the *BJS* invites submission of definitive manuscripts from papers presented at the meeting. These will be subjected to the normal review process of the Journal and those accepted will be published in a dedicated Eurosurgery issue.

Papers from the 1992 meeting will be appearing in a special issue in March 1993. The Editors encourage all contributors at Eurosurgery '93 to submit their contribution in an appropriate form to the *BJS*; detailed advice on preparation of manuscripts can be found in the Instructions to Authors at the back of each issue.

The Journal wishes every success to Eurochirurgie/Eurosurgery and the Editors join The Royal College of Surgeons of England and the numerous associated societies in welcoming European surgeons to London in September of this year.

C. D. Johnson
Associate Editor

Br. J. Surg. 1993, Vol. 80, February, 141–142

Screening for breast cancer

Screening for breast cancer by mammography is the only method of screening for malignancy that has been demonstrated to be of value by rigorous randomized trials. Current data indicate that 1 per cent of women in the 50–70 years age group could have their death postponed by screening and that the mortality rate from breast cancer can be reduced by as much as 40 per cent in women attending regularly for breast screening[1]. It is for this reason that routine mammographic screening for breast cancer in defined age groups is gradually being introduced throughout the Western world. Other techniques of breast screening, such as clinical examination, teaching breast self-examination and breast ultrasonography, have not been shown to be of value[2]. While the value of mammographic screening is now generally accepted, a number of controversial issues still remain.

Although consistent survival benefit has been demonstrated only in women over the age of 50 years, in some programmes younger women are being screened. In the light of currently available information, screening of these younger women cannot be supported and should not be offered unless as part of a specific study programme. While two-view mammography reduces the number of women recalled for assessment and slightly increases overall sensitivity[2], it doubles the dose of radiation; it is estimated that screening by one-view mammography induces 1 cancer per year after 10 years for every 2 million women screened. Debate continues on whether breast screening by mammography should be by one or two views, but in any national programme clear guidelines should be established and adhered to. The current situation in the UK, where government guidelines are that screening should be by single-view mammography, is that more than 40 per cent of units are screening using two views. This is totally unsatisfactory; it leads to confusion on the part of the public and among the individuals working in the units concerned. The most appropriate interval between mammographic screens is yet to be determined. Although from a cost–benefit point of view (cost per year of life gained and cost of quality-adjusted year of life saved) screening at intervals of 3 years of women aged 50–64 years appears to be the most attractive policy[3], the interval cancer rate climbs rapidly between the second and third year after the initial screen. This suggests that a 3-year interval is too long[4]. In contrast, annual mammography is almost certainly too frequent and the optimum frequency of screening is probably 2 years.

There has been a dramatic increase in the number of mammography units throughout the world over the past 10 years. Although units in countries that have government-led programmes have the quality of their mammography audited, this is not so for many of the rest. To ensure optimal benefits from screening it is imperative not only that the mammography is of the highest quality but also that patients recalled as a result of screening are assessed and treated appropriately. At present, few guidelines exist on assessment of screen-detected lesions and their subsequent treatment. For this reason a consensus conference has been organized by the European Society of Mastology and will take place during February 1993 in Paris. Clear guidelines on quality control of mammography, subsequent diagnostic assessment and appropriate treatment protocols for carcinomas detected by screening will follow.

The greatest proportion of deaths from breast cancer occurs between the ages[2] of 44 and 50 years. It is unfortunate that in this age group screening for breast cancer by mammography has not been shown to be of benefit. Data from family history studies indicate that genetic factors are implicated in some women, particularly in those who develop breast cancer at an early age. Current attention is centred on the long arm of chromosome 17, where there is a gene that in some families is associated with hereditary breast cancer[5]. It appears that between 1 and 6 per cent of patients with breast cancer have a genetic abnormality on the long arm of chromosome 17; this figure increases[6] to between 4 and 20 per cent in women who develop breast cancer under the age of 45 years. Within the next few years it will be possible to screen women who have a first-degree relative affected with breast cancer to identify individuals who are carrying the abnormal gene and who are therefore at very high

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risk of developing breast cancer. How to counsel patients identified as having a genetic abnormality and how they should be managed are issues currently being debated. However, it is hoped that genetic screening will have some impact on the death rate from breast cancer in women under the age of 50 years.

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1. Day NE. Screening for breast cancer. In: Stewart HJ, Anderson TJ, Forrest APM, eds. *Breast Disease – New Approaches. Br Med Bull* 1991; 47: 400–15.
2. Forrest APM. *Breast Cancer: the Decision to Screen.* London: Nuffield Provincial Hospital Trust, 1990.
3. Fraser N, Clarke P. Cost-effectiveness of breast cancer screening. *Breast* 1992; 1: 169–72.
4. Tabar L, Faberberg G, Day NE, Homberg L. What is the optimal interval between mammographic screening: an analysis based on the latest results of the Swedish two-county breast cancer screening trial. *Br J Cancer* 1987; 55: 547–51.
5. Hall JM, Lee MK, Newman B *et al.* Linkage of early onset familial breast cancer to chromosome 17q21. *Science* 1990; **250**: 1684–9.
6. Porter DE, Steel M. Recent advances in the genetics of heritable breast cancer. *Dis Markers* 1993 (in press).

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Future directions for conservative treatment of gallbladder calculi

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Recent conservative gallstone treatments provide rapid relief from symptoms, but all have a potential for stone recurrence. They are indicated in patients who are unfit or unwilling to undergo cholecystectomy. Wider application will depend on selection of patients who are at least risk of recurrence, or on development of effective prophylactic strategies.

Cholesterol gallstones form because of abnormalities in hepatic and gallbladder function[1,2]. Conventional cholecystectomy removes existing gallstones, interrupts the pathophysiological process and prevents recurrence. Minicholecystectomy[3] and laparoscopic cholecystectomy[4] have been developed to reduce surgical trauma while achieving the same therapeutic objectives. Prospective randomized trials comparing laparoscopic with conventional cholecystectomy are in progress.

Parallel with these developments, others have investigated the efficacy of removing the gallstones alone using techniques that either avoid surgery altogether[5,6] or are minimally invasive[7,8]. Such conservative treatments carry a potential for gallstone recurrence because they do not permanently interrupt the lithogenic process. At present, these treatments are indicated in patients with symptomatic gallstones who are either unfit or unwilling to undergo major surgery. In addition, increasing numbers of patients are prepared to accept a risk of recurrence in return for less invasive treatment[9,10]. The principal factor preventing more widespread adoption of conservative gallstone treatments is inability to define the risk of recurrence in individual patients. This paper examines the efficacy of these treatments and considers the challenges of predicting or preventing recurrence.

Asymptomatic gallbladder calculi

Population studies demonstrate that most people with gallbladder calculi have never had symptoms[11,12]; only 18 per cent will develop symptoms within 20 years of calculi forming[13] and the risk decreases with time. A complication, such as acute cholecystitis, cholangitis or pancreatitis, is an unlikely first presentation of previously asymptomatic calculi[13,14]. Prophylactic conventional cholecystectomy is generally not warranted on grounds of either health or cost in patients with 'silent' gallstones[15]. Laparoscopic cholecystectomy or conservative treatments are unlikely to be viewed any differently in this situation.

Relief of symptoms

Treatment is indicated at present only for symptomatic cholecystolithiasis. Conventional cholecystectomy relieves biliary colic in the majority of patients. Some remain symptomatic after cholecystectomy because the symptoms were not caused by gallstones; in others persistent symptoms may be related to an increased incidence of alkaline gastritis and gastro-oesophageal reflux[16,17].

It is now clear that both cholecystolithotomy and extracorporeal shockwave lithotripsy (ESWL) are also effective in relieving symptoms of gallbladder calculi in a majority of patients[10,18,19]. Indeed, with ESWL biliary pain is uncommon more than 2 months after starting treatment[10]. This suggests that it is the presence of calculi or, perhaps, their size rather than the diseased gallbladder itself that is responsible for symptoms. Recurrent gallstones are frequently asymptomatic and, arguably, do not require treatment[19–22].

Gallstone clearance

In general, more invasive treatments achieve gallstone clearance more rapidly and to a greater degree than less invasive methods. Oral bile acid therapy is an inefficient and expensive means of treating gallstones[5]. Even in highly selected patient groups, ursodeoxycholic acid has been reported[23] to achieve complete dissolution in only 30 per cent and partial dissolution in a further 30 per cent after 2 years. In contrast, when oral bile acid therapy is combined with ESWL, complete gallstone clearance may be expected within 2 years in up to 90 per cent of patients with a single cholesterol stone in a functioning gallbladder[10]. Even better results have been reported by Thistle *et al.*, who observed more than 95 per cent dissolution of cholesterol stones in 72 of 75 patients over a mean 12·5 h using methyl-*t*-butyl ether instilled into the gallbladder[24]. Finally, cholecystolithotomy, performed either using readily available surgical or radiological techniques[7,25] or laparoscopically[8], provides a simple and rapid means of removing gallstones. Moreover, cholecystolithotomy is applicable to stones of any chemical composition whereas oral dissolution is effective only for cholesterol calculi[9].

Gallstone recurrence

Although long-term recurrence rates as high as 61 per cent have been reported after oral bile acid therapy[21,26], rates as low as 11 per cent over 3 years are anticipated after ESWL for a single calculus in a functioning gallbladder[27]. While recurrence rates of up to 83 per cent have been reported after open cholecystolithotomy[20], short-term follow-up suggests that minimally invasive cholecystolithotomy may be associated with a lower recurrence rate[18]. This may be because patients selected for treatment have contracting gallbladders, operative trauma is less and there is no intraluminal suture line to act as a nidus for recurrence. Reliable long-term results are awaited.

A key issue when considering these data is whether recurrences are genuinely new calculi or merely growth from retained debris of previous stones. In bile supersaturated with cholesterol, the presence of crystals, stone fragments, non-cholesterol matrix, or cellular debris favours cholesterol nucleation. Adequate removal of such nucleating material is a prerequisite for consideration of true *de novo* recurrence. In particular, the high recurrence rates reported soon after dissolution may reflect the limitations of oral cholecystography in determining the endpoint of treatment, rather than genuine recurrence[28]. This interpretation is supported by the observation[29] that calculi recurring after oral bile acid therapy occur predominantly in the first 5 years. Ultrasonography is

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superior to oral cholecystography for both defining gallstone clearance after oral dissolution and detecting recurrence[28,30,31]; *in vitro* studies[32] indicate that it is now possible to detect stone fragments as small as 1·5 mm. Despite the use of ultrasonography, however, recurrences after treatment of single calculi using ESWL tend to be multiple, suggesting that incomplete clearance of gallstone debris may still go undetected[19,27]. Much depends on the commitment and skill of the ultrasonographer[33]. After ESWL, adequacy of fragmentation may be particularly difficult to determine if the stone burden is large[34,35].

Unlike dissolution therapies or ESWL, which depend on the resolution of radiological techniques, gallstone clearance at cholecystolithotomy may be confirmed visually or endoscopically[7,8]. Whether this translates into improved clearance and reduced recurrence rates is uncertain.

Intermittent lithogenesis

Retention of the gallbladder is not inevitably followed by gallstone recurrence; therefore in many patients the lithogenic process, or at least its initiation, is discontinuous[21,26]. This is supported by the observations that cholesterol crystals and biliary sludge (a prestone phase) are frequently intermittent[36,37], and that gallstones are often single or belong to groups of similar size. Whereas some people have an ongoing lithogenic tendency, in others gallstones are the surviving evidence of a lithogenic process that has long since ceased. Recognized initiating factors include pregnancy, rapid weight loss and convalescence from abdominal surgery[36,38,39]. The challenge facing clinicians interested in using conservative gallstone therapies is to devise an index of the risk of gallstone recurrence in individual patients, or to develop effective methods of prophylaxis against recurrences that are applicable to all patients with gallstones.

Index of the risk of gallstone recurrence

Differentiation between patients at low or high risk of gallstone recurrence would allow the best use of therapeutic options. The number of stones has some predictive value, in that recurrence is more likely after treatment of multiple calculi[26,31]. As regards lithogenesis, dissolution studies have demonstrated that, following cessation of oral bile acid therapy, in most patients the liver reverts to secreting cholesterol-supersaturated bile[40]. This in itself, however, is insufficient cause for gallstones[41]. Abnormalities in gallbladder function are essential for stone formation[2,42] and probably determine whether there will be recurrence. Cholesterol gallstone formation is characterized by impaired gallbladder emptying[43], altered absorptive capacity[1,44,45] and production of cholesterol-nucleating agents[42,46]. If gallbladder function is normal then, it is argued, stone recurrence should not occur.

Although many patients with gallstones have impaired gallbladder emptying, in more than half, emptying is normal[43]. Gallbladder emptying has been reported to improve after dissolution therapy[47], but no enhancement was noted following ESWL[48]. In the latter study gallbladder emptying was measured by the highly reliable sum-of-cylinders method[49,50]. Gallbladder secretion, release of nucleating agents, and the nucleating time of gallbladder bile may be estimated from samples of duodenal bile[39,51] or, preferably, by percutaneous gallbladder puncture[52]. In patients without macroscopic gallstones increased total lipid and protein concentrations are associated with crystals[45]. In those with gallstones the presence of crystals in addition to calculi correlates with the protein concentration of gallbladder bile[53], while the *in vitro* nucleation time correlates with concentrating capacity[54]. Nucleation times are considerably lower in gallbladder bile from patients with multiple rather than solitary stones[55]. These studies provide preliminary evidence that increased total lipid and protein concentrations in gallbladder bile indicate an ongoing lithogenic tendency. Conversely, the combination of low total lipid and protein concentrations, longer nucleation time, absence of cholesterol crystals, and normal gallbladder emptying in patients with a solitary gallstone may indicate a reduced risk of stone recurrence. Further research is required to determine which parameters have the best predictive value. Meanwhile, the term 'functioning gallbladder', which has been used to imply normal physiological gallbladder function, should be replaced by a more precise description of what is being measured.

Prevention of gallstone recurrence

Prophylaxis of gallstone recurrence must be effective against both regrowth from stone debris and new stone formation. The widest benefit will most likely derive from intervention in the production of supersaturated bile or its nucleation. Obliteration of the gallbladder lumen is a further option in patients undergoing percutaneous or open cholecystolithotomy.

Reducing biliary cholesterol saturation

Although therapeutic doses of chenodeoxycholic acid reduce biliary cholesterol saturation and cause cholesterol gallstones to dissolve, continuous low-dose chenodeoxycholic acid (375 mg day^{-1}) is ineffective in preventing recurrence[56]. High-dose ursodeoxycholic acid (1200 mg day^{-1}) prevented new gallstone formation in patients undergoing rapid weight loss[39]. In one report[26] low-dose ursodeoxycholic acid (300 mg day^{-1}) significantly reduced the recurrence rate after oral dissolution therapy in patients younger than 50 years. However, the British–Belgian trial found that, although continuous low-dose ursodeoxycholic acid therapy (3 mg kg^{-1} day^{-1}) halved the gallstone recurrence rate, this was not statistically significant[31]. Long-term use of oral bile salts is not a cost-effective means of preventing recurrence.

Reducing dietary cholesterol intake to 100 mg day^{-1} (one-sixth of normal) has no significant independent effect on biliary cholesterol saturation in patients with cholesterol gallstones, although it enhances the action of oral bile salts[57]. High-fibre diets lower the cholesterol saturation of supersaturated gallbladder bile[58,59], whereas refined carbohydrate increases cholesterol saturation[60]. The prospect that simple dietary manipulation might prevent gallstone recurrence has obvious attractions. However, in a preliminary report, a combination of increased fibre (>30 g day^{-1}) and reduced refined carbohydrate (<15 g day^{-1}) was unable to prevent gallstone recurrence after oral dissolution therapy[31]. Diets rich in legumes markedly increase biliary cholesterol saturation in health[61]; the effects of a low-legume intake on gallstone formation are unknown. Competitive inhibitors of cholesterol synthesis such as simvastatin and lovastatin[62,63] also reduce biliary cholesterol saturation. Moreover, use of lovastatin together with ursodeoxycholic acid causes a greater reduction in biliary cholesterol saturation than use of bile acid alone[63]. To date, there is one report of rapid gallstone dissolution using this combination[64].

Prokinetic agents

Intravenous cholecystokinin administered daily has been reported to prevent formation of gallbladder sludge in patients in an intensive care unit[65]. Oral erythromycin (500 mg), which has motilin-like activity, increases gallbladder emptying in both controls and patients who have undergone cholecystolithotomy[66]. Indomethacin enhances postprandial gallbladder emptying after cholecystolithotomy[67], in line with the proposed role of prostaglandins as mediators of gallbladder stasis during lithogenesis[68,69]. Prokinetic agents may be expected to hasten removal of gallstone debris following ESWL and facilitate removal of non-cholesterol components of calculi during dissolution therapy. This approach could prove especially useful in the recovery period after cholecystolithotomy, when gallbladder emptying is likely to be impaired.

Inhibition of cholesterol nucleation

Rapid nucleation of cholesterol in the gallbladder appears to be central to the lithogenic process[42]. Of the potential nucleating agents, most attention has focused on mucin and smaller glycoproteins, and calcium[70–73]. To date only mucin, the macromolecular glycoprotein of mucus gel, is known to increase in concentration before cholesterol crystal formation, and this evidence derives principally from animal models[74]. Interestingly, however, human biliary sludge consists of thick mucus gel with cholesterol crystals[75]. Non-steroidal anti-inflammatory drugs (NSAIDs) have been used to prevent mucin hypersecretion and lithogenesis in experimental models, but their efficacy is questionable[76,77]. Aspirin reduces gallbladder mucosal mucin in humans[78] but has not produced consistent effects on gallstone formation. In a retrospective study, Hood *et al.*[79] observed no recurrences among patients who regularly took NSAIDs (mainly aspirin) after successful oral dissolution therapy, but Broomfield *et al.*[39] noted no significant protective effect in a small prospective study of patients undergoing rapid weight loss. Although there is at present no compelling evidence that pharmacological intervention interferes with cholesterol nucleation in humans, this remains a promising area for further research.

Mucosal destruction and gallbladder obliteration

Cholecystolithotomy followed by gallbladder obliteration would enable complete treatment to be administered on a single occasion. The cystic duct can be occluded by minicoils, balloon catheters or bipolar electrocoagulation and the mucosa destroyed using sclerosants, toxins or diathermy[80–83]. Potential problems include damage to the duct system, and reopening and re-epithelialization of the gallbladder. Cuschieri *et al.* reported moderate success in animals using a biliary balloon catheter to occlude the cystic duct together with sodium carbonate as a gallbladder sclerosant[80]. Becker *et al.*[81] used bipolar electrocoagulation to occlude the cystic duct and ablated the gallbladder mucosa with 95 per cent ethanol and 3 per cent sodium tetradecyl sulphate. This group has reported good results[84] in nine patients at a mean of 14 months.

Conclusions

Patients with gallstones are not a homogeneous group. Management decisions should ideally be based on the characteristics of the patient, the gallbladder and the gallstones. High recurrence rates previously reported following conservative gallstone therapy may partly reflect incomplete treatment. Development of an index for the risk of stone recurrence in individuals would allow more appropriate selection of patients for cholecystectomy or conservative treatment. Future advances are more likely to depend on effective prophylaxis of gallstone recurrence than on further therapeutic innovations. For the community at large, this line of research also represents the best chance of yielding methods for preventing gallstone formation in the first place.

References

1. Carey MC, Small DM. The physical chemistry of cholesterol solubility in bile. Relationship to gallstone formation and dissolution in man. *J Clin Invest* 1978; **61**: 998–1026.
2. LaMorte WW, Schoetz DJ, Birkett DH, Williams LF. The role of the gallbladder in the pathogenesis of cholesterol gallstones. *Gastroenterology* 1979; **77**: 580–92.
3. O'Dwyer PJ, Murphy JJ, O'Higgins NJ. Cholecystectomy through a 5-cm subcostal incision. *Br J Surg* 1990; **77**: 1189–90.
4. Dubois F, Icard P, Berthelot G, Levard H. Coelioscopic cholecystectomy. *Ann Surg* 1990; **211**: 60–2.
5. Schoenfield JL, Lachin JM, the Steering Committee, the National Cooperative Gallstone Study Group. Chenodiol (chenodeoxycholic acid) for dissolution of gallstones: the National Cooperative Gallstone Dissolution Study: a controlled trial of efficacy and safety. *Ann Intern Med* 1981; **95**: 257–82.
6. Sauerbruch T, Delius M, Paumgartner G *et al.* Fragmentation of gallstones by extracorporeal shock waves. *N Engl J Med* 1986; **314**: 818–22.
7. Kellett MJ, Wickham JE, Russell RC. Percutaneous cholecystolithotomy. *BMJ* 1988; **296**: 453–5.
8. Majeed AW, Reed MWR, Johnson AG. Minimally invasive gallbladder surgery using a new instrument: the laparocholecystoscope. *Br J Surg* 1990; **77**: 1423.
9. Chiverton SG, Inglis A, Hudd C, Kellett MJ, Russell RCG, Wickham JEA. Percutaneous cholecystolithotomy: the first 60 patients. *BMJ* 1990; **300**: 1310–12.
10. Sackmann M, Pauletzki J, Sauerbruch T, Holl J, Schelling G, Paumgartner G. The Munich gallbladder lithotripsy study. Results of the first five years with 711 patients. *Ann Intern Med* 1991; **114**: 290–6.
11. Heaton KW, Braddon FE, Mountford RA, Hughes AO, Emmett PM. Symptomatic and silent gallstones in the community. *Gut* 1991; **32**: 316–20.
12. Rome Group for Epidemiology and Prevention of Cholelithiasis. The epidemiology of gallstone disease in Rome, Italy. Part 1. Prevalence data in men. *Hepatology* 1988; **8**: 904–6.
13. Gracie WA, Ransohoff DF. The natural history of silent gallstones. The innocent gallstone is not a myth. *N Engl J Med* 1982; **307**: 798–800.
14. McSherry CK, Ferstenberg H, Calhoun WF, Laham E, Virshup M. The natural history of diagnosed gallstone disease in symptomatic and asymptomatic patients. *Ann Surg* 1985; **202**: 59–63.
15. Ransohoff DF, Gracie WA, Wolfenson LB, Neuhauser D. Prophylactic cholecystectomy or expectant management for silent gallstones. A decision analysis to assess survival. *Ann Intern Med* 1983; **99**: 199–204.
16. Johnson AG. Pyloric function and gallstone dyspepsia. *Br J Surg* 1972; **59**: 449–54.
17. Brown TH, Walton G, Cheadle WG, Larson GM. The alkaline shift in gastric pH after cholecystectomy. *Am J Surg* 1989; **157**: 58–65.
18. Cheslyn-Curtis S, Donald J, Ainley C, Lees WR, Russell RCG. Gallstone recurrence following percutaneous cholecystolithotomy. *Br J Surg* 1990; **77**: 1423 (Abstract).
19. Lee SH, Burhenne HJ. Persistence of symptoms after gallbladder clearance with cholecystolithotripsy. *Gut* 1991; **32**: 536–9.
20. Norrby S, Schonebeck J. Long-term results with cholecystolithotomy. *Acta Chirurgica Scandinavica* 1970; **136**: 711–13.
21. Ruppin DC, Dowling RH. Is recurrence inevitable after gallstone dissolution by bile-acid treatment? *Lancet* 1982; **i**: 181–5.
22. Gibney RG, Chow K, So CB, Rowley VA, Cooperberg PL, Burhenne HJ. Gallstone recurrence after cholecystolithotomy. *AJR Am J Roentgenol* 1989; **53**: 287–9.
23. Fromm H, Roat JW, Gonzalez V, Sarva RP, Farivar S. Comparative efficacy and side effects of ursodeoxycholic and chenodeoxycholic acids in dissolving gallstones: a double-blind controlled study. *Gastroenterology* 1983; **85**: 1257–64.
24. Thistle JL, May GR, Bender CE *et al.* Dissolution of cholesterol gallbladder stones by methyl *tert*-butyl ether administered by percutaneous transhepatic catheter. *N Engl J Med* 1989; **320**: 633–9.
25. Hamilton S, Leahy AL, Darzi A, Keane FB. Biliary intervention via minicholecystostomy. *Clin Radiol* 1990; **42**: 418–22.
26. Villanova N, Bazzoli F, Taroni F *et al.* Gallstone recurrence after successful oral bile acid treatment. *Gastroenterology* 1989; **97**: 726–31.
27. Sackman M, Ippisch E, Sauerbruch T, Holl J, Brendel W, Paumgartner G. Early gallstone recurrence rate after successful shock-wave therapy. *Gastroenterology* 1990; **98**: 392–6.
28. Somerville KW, Rose DH, Bell GD, Ellis WR, Knapp DR. Gall-stone dissolution and recurrence: are we being misled? *BMJ* 1982; **284**: 1295–7.
29. O'Donnell LDJ, Heaton KW. Recurrence and re-recurrence of gallstones after medical dissolution: long term follow up. *Gut* 1988; **29**: 655–8.
30. Gleeson D, Ruppin DC, the British Gallstone Study Group. Discrepancies between cholecystography and ultrasonography in the detection of recurrent gallstones. *J Hepatol* 1985; **1**: 597–607.
31. Hood K, Gleeson D, Ruppin D, Dowling H. Can gallstone recurrence be prevented? The British/Belgian post-dissolution trial. *Gastroenterology* 1988; **94**: A548.
32. Garra BS, Davros WJ, Lack EE, Horii SC, Silverman PM, Zeman RK. Visibility of gallstone fragments at ultrasound fluoroscopy: implications for monitoring gallstone lithotripsy. *Radiology* 1990; **174**: 343–7.

33. Brink JA, Simeone JF, Mueller PR *et al.* Routine sonographic techniques fail to quantify gallstone size and number: a retrospective study of 111 surgically proved cases. *AJR Am J Roentgenol* 1989; **153**: 503–6.
34. Sackmann M, Delius M, Sauerbruch T *et al.* Shockwave lithotripsy of gallbladder stones: the first 175 patients. *N Engl J Med* 1988; **318**: 393–7.
35. Mathieson JR, So CB, Malone DE, Becker CD, Burhenne HJ. Accuracy of sonography for determining the number and size of gallbladder stones before and after lithotripsy. *AJR Am J Roentgenol* 1989; **153**: 977–80.
36. Bolondi L, Gaiani S, Testa S, Labo G. Gallbladder sludge formation during prolonged fasting after gastrointestinal surgery. *Gut* 1985; **26**: 734–8.
37. Lee SP, Maher K, Nicholls JF. Origin and fate of biliary sludge. *Gastroenterology* 1988; **94**: 170–6.
38. Rome Group for Epidemiology and Prevention of Cholelithiasis. The epidemiology of gallstone disease in Rome, Italy. Part 2. Factors associated with the disease. *Hepatology* 1988; **8**: 907–13.
39. Broomfield PH, Chopra R, Sheinbaum RC *et al.* Effects of ursodeoxycholic acid and aspirin on the formation of lithogenic bile and gallstones during loss of weight. *N Engl J Med* 1988; **319**: 1567–72.
40. Ruppin DC, Murphy GM, Dowling RH, the British Gallstone Study Group. Gall stone disease without gall stones – bile acid and bile lipid metabolism after complete gall stone dissolution. *Gut* 1986; **27**: 559–66.
41. Holzbach RT, Marsh M, Olsezwski M, Holan K. Cholesterol solubility in bile: evidence that supersaturated bile is frequent in healthy man. *J Clin Invest* 1973; **52**: 1467–79.
42. Holan KR, Holzbach RT, Hermann RE, Cooperman AM, Claffey WJ. Nucleation time: a key factor in the pathogenesis of cholesterol gallstone disease. *Gastroenterology* 1979; **77**: 611–17.
43. Pomeranz IS, Shaffer EA. Abnormal gallbladder emptying in a subgroup of patients with gallstones. *Gastroenterology* 1985; **88**: 787–91.
44. Conter RL, Roslyn JJ, Porter-Fink V, DenBesten L. Gallbladder absorption increases during early cholesterol gallstone formation. *Am J Surg* 1986; **151**: 184–90.
45. Strasberg SM, Toth JL, Gallinger S, Harvey PR. High protein and total lipid concentration are associated with reduced metastability of bile in an early stage of cholesterol gallstone formation. *Gastroenterology* 1990; **98**: 739–46.
46. Gollish SH, Burnstein MJ, Ilson RG, Petrunka CN, Strasberg SM. Nucleation of cholesterol monohydrate crystals from hepatic and gallbladder bile of patients with cholesterol gallstones. *Gut* 1983; **24**: 836–44.
47. Sylwestrowicz TA, Shaffer EA. Gallbladder function during gallstone dissolution. Effect of bile acid therapy in patients with gallstones. *Gastroenterology* 1988; **95**: 740–8.
48. Spengler U, Sackmann M, Sauerbruch T, Holl J, Paumgartner G. Gallbladder motility before and after extracorporeal shock-wave lithotripsy. *Gastroenterology* 1989; **96**: 860–3.
49. Lanzini A, Northfield TC. Assessment of motor functions of the gallbladder. *J Hepatol* 1989; **9**: 383–91.
50. Stolk MJF, van Erpecum KJ, van Berge Henegouwen GP, Kesselring OFHW, Hopman WPM. Gallbladder volume and contraction measured by sum-of-cylinders method compared with ellipsoid and area–length methods. *Acta Radiol* 1990; **31**: 591–6.
51. Marks JW, Broomfield P, Bonorris GG, Schoenfield LJ. Factors affecting the measurement of cholesterol nucleation in human gallbladder and duodenal bile. *Gastroenterology* 1991; **101**: 214–19.
52. Janowitz P, Swobodnik W, Wechsler JG, Zoller A, Kuhn K, Ditschuneit H. Comparison of gall bladder bile and endoscopically obtained duodenal bile. *Gut* 1990; **31**: 1407–10.
53. Jungst D, Lang T, von Ritter C, Paumgartner G. Role of high total protein in gallbladder bile in the formation of cholesterol gallstones. *Gastroenterology* 1991; **100**: 1724–9.
54. Jungst D, Lang T, Paumgartner G. Relation between lipid concentration and nucleation time in gallbladder bile of patients with cholesterol gallstones. *Gastroenterology* 1990; **98**: A252.
55. van Erpecum KJ, van Berge Henegouwen GP, Stoelwinder B, Schmidt YM, Willekens FL. Bile concentration is a key factor for nucleation of cholesterol crystals and cholesterol saturation index in gallbladder bile of cholesterol gallstone patients. *Hepatology* 1990; **11**: 1–6.
56. Marks JW, Lan S-P, the Steering Committee, the National Cooperative Gallstone Study Group. Low-dose chenodiol to prevent gallstone recurrence after dissolution therapy. *Ann Intern Med* 1984; **100**: 376–81.
57. Maudgal DP, Bird R, Blackwood WS, Northfield TC. Low-cholesterol diet: enhancement of effect of CDCA in patients with gallstones. *BMJ* 1978; **ii**: 851–3.
58. Pomare EW, Heaton KW, Low-Beer TS, Espiner HJ. The effect of wheat bran upon bile salt metabolism and upon the lipid composition of bile in gallstone patients. *Am J Dig Dis* 1976; **21**: 521–6.
59. Marcus SN, Heaton KW. Effects of a new concentrated wheat fibre preparation on intestinal transit, deoxycholic acid metabolism and the composition of bile. *Gut* 1986; **27**: 893–900.
60. Thornton JR, Emmett PM, Heaton KW. Diet and gall stones: effects of refined and unrefined carbohydrate diets on bile cholesterol saturation and bile acid metabolism. *Gut* 1983; **24**: 2–6.
61. Nervi F, Covarrubias C, Bravo P *et al.* Influence of legume intake on biliary lipids and cholesterol saturation in young Chilean men. *Gastroenterology* 1989; **96**: 825–30.
62. Duane WC, Hunninghake DB, Freeman ML, Pooler PA, Schlasner LA, Gebhard RL. Simvastin, a competitive inhibitor of HMG-CoA reductase, lowers cholesterol saturation index of gallbladder bile. *Hepatology* 1988; **8**: 1147–50.
63. Logan GM, Duane WC. Lovastatin added to ursodeoxycholic acid further reduces biliary cholesterol saturation. *Gastroenterology* 1990; **98**: 1572–6.
64. Bateman MC. Simvastatin and ursodeoxycholic acid for rapid gallstone dissolution. *Lancet* 1990; **336**: 1196.
65. Sitzmann JV, Pitt HA, Steinborn PA, Pasha ZR, Sanders RC. Cholecystokinin prevents parenteral nutrition induced biliary sludge in humans. *Surg Gynecol Obstet* 1990; **170**: 25–31.
66. Catnach SM, Fairclough PD, Trembath RC *et al.* Effect of erythromycin on gallbladder motility in normal subjects and subjects with gallstones. *Gastroenterology* 1992; **102**: 2071–6.
67. O'Donnell LDJ, Wilson P, Guest P *et al.* Indomethacin and post-prandial gallbladder emptying. *Lancet* 1992; **339**: 269–71.
68. Kuchenbecker SL, Doty JE, Pitt HA, DenBesten L. Salicylate prevents gallbladder stasis and cholesterol gallstones in the prairie dog. *Surgical Forum* 1981; **32**: 154–5.
69. Chapman WC, Peterkin GA, LaMorte WW, Williams LF. Alterations in biliary motility correlate with increased gallbladder prostaglandin synthesis in early cholelithiasis in prairie dog. *Dig Dis Sci* 1989; **34**: 1420–4.
70. Levy PF, Smith BF, LaMont JT. Human gallbladder mucin accelerates nucleation of cholesterol in artificial bile. *Gastroenterology* 1984; **87**: 270–5.
71. Lee TJ, Smith BF. Bovine gallbladder mucin promotes cholesterol crystal nucleation from cholesterol-transporting vesicles in supersaturated model bile. *J Lipid Res* 1989; **30**: 491–8.
72. Groen AK, Noordham C, Drapers JAG, Egbers P, Jansen PLM, Tytgat GNJ. Isolation of a potent cholesterol nucleation-promoting activity from human gallbladder bile: role in the pathogenesis of gallstone disease. *Hepatology* 1990; **11**: 525–33.
73. Kibe A, Dudley MA, Halpern Z, Lynn MP, Breuer AC, Holzbach RT. Factors affecting cholesterol monohydrate crystal nucleation time in model systems of supersaturated bile. *J Lipid Res* 1985; **26**: 1102–11.
74. Lee SP, LaMont JT, Carey MC. Role of gallbladder mucus hypersecretion in the evolution of cholesterol gallstones: studies in the prairie dog. *J Clin Invest* 1981; **67**: 1712–23.
75. Lee SP, Nicholls JF. Nature and composition of biliary sludge. *Gastroenterology* 1986; **90**: 677–86.
76. Lee SP, Carey MC, LaMont JT. Aspirin prevention of cholesterol gallstone formation in the prairie dog. *Science* 1981; **211**: 1429–31.
77. O'Leary DP, LaMorte WW, Scott TE, Booker ML, Stevenson J. Inhibition of prostaglandin synthesis fails to prevent gallbladder mucin hypersecretion in the cholesterol-fed prairie dog. *Gastroenterology* 1991; **101**: 812–20.
78. Rhodes M, Allen A, Dowling RH, Murphy G, Lennard TWJ. Inhibition of human gall bladder mucus synthesis in patients undergoing cholecystectomy. *Gut* 1992; **33**: 1113–17.
79. Hood K, Ruppin DC, Gleeson D, Dowling RH. Prevention of gallstone recurrence by non-steroidal anti-inflammatory drugs. *Lancet* 1988; **ii**: 1223–5.
80. Cuschieri A, Abdel Ghany AA, Holley MP. Successful chemical cholecystectomy: a laparoscopic guided technique. *Gut* 1989; **30**: 1786–94.
81. Becker CD, Quenville NF, Burhenne HJ. Gallbladder ablation through radiologic intervention: an experimental alternative to

cholecystectomy. *Radiology* 1989; **171**: 235–40.
82. Uchiyama N, Stridbeck H, Stenram U. Chemical sclerosis of the gallbladder. An experimental study in pigs of the effect of absolute ethanol and polidocanol on gallbladder epithelium. *Acta Radiol* 1989; **30**: 427–31.
83. Leahy AL, McCollum PT, O'Gorman S *et al.* Cystic duct obliteration and gallbladder mucosal destruction: a feasible alternative to cholecystectomy. *Br J Surg* 1991; **78**: 1321–4.
84. Burhenne HJ, Lee SH, Fache JS, Stoller JL, Becker CD. Radiologic gallbladder ablation: two-year follow up. *Radiology* 1990; **176**: 687–90.

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Announcement

Frank Glenn Travelling Fellowship 1993

The International Hepato-Biliary-Pancreatic Association invites applications for the above travelling Fellowship. A stipend of 500 SFr is available to subsidize a young investigator in the field of hepatobiliary and pancreatic disorders. The applicant must be sponsored by a member of the Association. The stipend may be used to support a laboratory project and/or to subsidize travel expenses that are deemed appropriate to the field of investigation. Applicants must be under 40 years of age and should have an established record of at least one or several papers concerning liver, biliary or pancreatic disease.

Applications should be made in writing and should include the following:

1. A copy of the applicant's *curriculum vitae*.
2. A summary of 1–2 pages of a research protocol describing how the stipend is to be used.
3. A letter of nomination from a member of the IHBPA or the applicant's Department Chair.

Applications should be sent to: Professor A. Cuschieri, University Department of Surgery, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK. Telephone: (0382) 60111 Extn 2174; Fax: (0382) 641795.

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Pancreatic infection complicating acute pancreatitis

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Pancreatic infection is the leading cause of death from acute pancreatitis. Patients with severe necrotizing pancreatitis are most at risk. Early computed tomography and percutaneous fine-needle aspiration microbiology of areas of pancreatic necrosis enable early diagnosis. Pancreatic infection should be treated surgically, although sterile necrosis may be managed conservatively. The role of antimicrobial drugs is uncertain.

The incidence of acute pancreatitis in the UK ranges[1–6] from 47 to 238 cases per 10^6 population per year. Although most patients make an uneventful recovery, some develop serious complications and approximately 10 per cent die[1,2,3–11]. The mortality rate has remained largely unchanged over the past two decades despite improvements in general medical and intensive care. However, few patients now die from either cardiopulmonary or renal complications alone, and pancreatic infection with multiple organ failure is the single most frequent cause of mortality[10,12–16]. Thus many of the improvements in treatment have served only to change the mode of death[10].

At present, pancreatic infection tends to be diagnosed relatively late and surgical drainage and debridement offer the only hope of cure for these seriously ill patients. Surgery is associated with high morbidity and mortality rates and improvements in surgical or preoperative medical treatments are unlikely to reduce this risk significantly in the foreseeable future. However, increased awareness of pancreatic infection, with earlier diagnosis and treatment in centres with the necessary technology and expertise, may lead to an improvement. This paper reviews the epidemiology, pathogenesis and clinical features of pancreatic infection, and discusses the indications for surgical intervention and the options available.

Definitions and methods

Pancreatic infection is defined as the presence of bacteria or fungi multiplying in the pancreas and/or peripancreatic tissues and causing pathological change. Infected pancreatic necrosis is defined as a diffuse infection of necrotic pancreatic and/or peripancreatic tissues. Pancreatic abscess is defined as a localized collection of pus arising within or in the region of the gland and bounded by a wall of collagen and granulation tissue.

For the purposes of this review relevant articles were identified from Medline computer searches and lists of references from *Index Medicus*. Only infected necrosis or pancreatic abscess complicating acute pancreatitis was reviewed. Infected pancreatic pseudocysts (a discrete pancreatic or peripancreatic collection of fluid originating from the pancreas and bounded by a wall of collagen and granulation tissue) were excluded because they may have a different pathogenesis, carry a better prognosis, cause fewer complications and may be treated differently[17–19].

Epidemiology

It is difficult to be precise about the prevalence of pancreatic infection because many reports are from tertiary referral centres with a specialist interest in the disease[11,13,20–25]. It is estimated that acute necrotizing pancreatitis develops in 10–20 per cent of patients with acute pancreatitis[12,20,21,26,27], of whom about 30 per cent develop pancreatic infection[20,28–35]. Therefore, 3–6 per cent of all patients with acute pancreatitis develop infected pancreatic necrosis. In addition, pancreatic abscesses develop in 3–4 per cent of patients with acute pancreatitis[16,31,32,36–68]. Overall, pancreatic infection thus develops in 6–10 per cent of patients during, or shortly after, an attack of acute pancreatitis[12,16;21].

The median age of patients with a pancreatic abscess is 46 (range 10–89) years. The male:female ratio[31,36,39,41–54,56–60,62–65,69] is 2·7:1. The mean age and sex ratio appear to be similar for patients with infected pancreatic necrosis[22,29,37]. The young age and predominance of male patients may be because most of the series reviewed were from the USA.

A review of infected pancreatic necrosis and pancreatic abscess from the USA has been undertaken to ascertain the aetiology of the associated acute pancreatitis (*Table 1*)[31,32,36,39,42–47,50,51,53–61,63–66,70]. This allows for comparison to be made with the prevalence of each factor among all patients who develop acute pancreatitis in the USA[71]. This analysis suggests that patients with alcoholic pancreatitis have a relatively low risk of developing a pancreatic abscess, whereas those who develop postoperative or post-traumatic pancreatitis have a greater risk.

Pathology

In infected pancreatic necrosis the macroscopic appearance is one of soft friable grey-black necrotic tissue distributed throughout the gland. The entire pancreas may be involved. Frequently there are pancreatic haemorrhages and opaque yellow or grey fat necrosis in the mesentery, omentum and retroperitoneum[72–76]. Histologically such necrosis involves acinar cells, blood vessels, fibrous tissue, fat and the islets of Langerhans.

A pancreatic abscess consists of a collection of frank pus, or necrotic material, enclosed by an inflammatory capsule or pseudocapsule. There may be adjacent areas of necrotic tissue, haemorrhages and fat necrosis. Pancreatic abscesses may be single (38 per cent) or multiple (62 per cent), unilocular or multilocular[37,48,49,57,61]. Approximately 25 per cent of abscesses involve the entire gland, 30 per cent are right sided and related to the head of the gland, 23 per cent arise from the body, and 22 per cent are left sided and related to the pancreatic tail[43,48,49,60,63,64]. Abscesses may extend in any direction to involve adjacent structures including blood vessels, the transverse colon and the common bile duct.

Microbiology

Pancreatic abscesses are more frequently polymicrobial (57 per cent) than monomicrobial (43 per cent)[77]. The

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Table 1 *Aetiology of acute pancreatitis complicated by pancreatic abscess*

			Aetiology of pancreatitis			
Reference	Year	No. of abscesses	Alcoholic	Gallstones	Postoperative and post-traumatic	Other
Altemeier and Alexander[36]	1963	32	7	18	1	6
Farringer *et al.*[65]	1966	7	0	4	0	3
Steedman *et al.*[64]	1967	13	7	4	0	2
Bolooki *et al.*[63]	1968	74	40	7	21	6
Miller *et al.*[39]	1974	63	8	4	33	18
Camer *et al.*[61]	1975	84	6	21	48	9
Grace and State[70]	1976	9	8	0	0	1
Holden *et al.*[60]	1976	28	20	5	Excluded	3
Owens *et al.*[59]	1977	8	6	1	1	0
Paloyan *et al.*[58]	1978	7	4	0	3	0
Frey *et al.*[32]	1979	84	12	10	40	22
Donahue *et al.*[57]	1980	12	12	0	0	0
Berne and Donovan[56]	1981	7	7	0	0	0
Chang and Van Houden[55]	1981	7	3	1	3	0
Davidson and Bradley[54]	1981	17	14	2	0	1
Saxon *et al.*[53]	1981	21	6	4	5	6
Aranha *et al.*[51]	1982	20	10	0	9	1
Bradley and Fulenwider[50]	1984	21	15	1	0	5
Crass *et al.*[46]	1985	21	14	4	1	2
Sostre *et al.*[47]	1985	8	3	5	0	0
Warshaw and Jin[45]	1985	45	17	5	10	13
McClave *et al.*[44]	1986	21	10	4	4	3
Malangoni *et al.*[43]	1986	27	13	5	8	1
Wertheimer and Norris[31]	1986	10	5	2	2	1
Hurley and Vargish[42]	1987	18	2	6	5	5
Fink *et al.*[66]	1988	100	57	32	2	9
Percentage of total			40	19	27	15
Percentage of all patients with acute pancreatitis in the USA[71]			70	16	7	7

Table 2 *Comparative bacteriology of pancreatic abscesses with other infections*

	Escherichia coli	*Klebsiella*	Enterobacter	Enterococci	Other streptococci	Staphylococci	Anaerobes
Pancreatic abscess	35	19	9	23	18	7	9
Subphrenic abscess	96	21	—	67	—	8	83
Bacteraemia	22	8	2	5	20	17	17
Lithogenic bile	38	11	4	15	3	4	12

Values are percentages

organism most frequently cultured is *Escherichia coli*, which is found in 35 per cent of abscesses. Enterococci, *Klebsiella* and non-enteric streptococci are each found in about 20 per cent. Enterobacter, staphylococci, anaerobes and fungi are found in fewer than 10 per cent. The organisms isolated from infected pancreatic necrosis appear to be similar[22,23,27,29,37,78].

Pathogenesis

The species of pathogens isolated from the infected pancreas suggest an enteric origin[36,39,65,79–81]. Only the colon harbours the many different species of bacteria isolated from infected pancreata in significant numbers. However, the anaerobic bacteria that predominate in the colon are rarely isolated from patients with pancreatic infection, and the relative proportion of the different species of bacteria causing such infection more closely resembles that found in bile (*Table 2*)[82–85].

Animal studies have shown that bacteria may reach both the normal and inflamed gland from many sources including the colon, gallbladder and urinary tract. Bacteria may reach the pancreas via a number of different routes, such as the transcoelomic route, via the main pancreatic duct, or via the circulation[79,86–89]. In healthy animals contaminating bacteria are cleared from the pancreas without complications developing. It is only animals with inflamed glands that develop infection, and the infection rate is proportional to the extent of the pancreatic necrosis[90,91]. This suggests that, as with infection in other organs, the necrotic tissue is a haven where organisms multiply.

In addition, there is evidence for reduced host resistance to infection in acute pancreatitis. This possibility was first raised by Adham *et al.*, who showed that stimulating the reticulo-endothelial system reduced the mortality rate of mice fed a choline-deficient ethionine-supplemented diet[92]. Recent studies in cats have shown that acute pancreatitis reduces the rate of clearance of *E. coli* from the circulation, suggesting impaired reticuloendothelial system function[93]. Little work has been carried out in humans. However, Curley *et al.* in 1991 reported that in patients with severe acute pancreatitis the proportion of CD4-positive (T helper) cells and of cells expressing major histocompatibility complex class I antigens were lower than in those with mild disease[94]. Although further work is needed, these reports suggest that patients with acute pancreatitis are immunocompromised in a way similar to those with extensive burns, obstructive jaundice, haemorrhagic shock or major trauma[95–101].

Diagnosis

Clinical features

Most patients with pancreatic infection complain of a constant severe upper abdominal pain that frequently radiates to the back or flank and is associated with nausea and vomiting[36,51,57,61,62,64]. A few present with a complication such as gastrointestinal haemorrhage, intestinal perforation, or fistula[30,36,37,39,45,49,51,57,60,61,64,80,102]. Some 80 per cent of patients are febrile[36,57,60–62,64,65] with pyrexia >38°C, spiking to 41°C. The abdomen is tender in 66 per cent and a mass palpable in 39 per cent. However, these symptoms and signs are non-specific and, clinically, pancreatic abscess, sterile or infected pancreatic necrosis, and sterile or infected pancreatic pseudocysts cannot be distinguished with confidence[10,16,31,36,39,41,43,45,47,48,51–55,57–66,70].

Investigations

Serum amylase concentration may be normal or raised. Persistent hyperamylasaemia may result from infection, pancreatic carcinoma or pancreatic pseudocyst[36]. Although 75 per cent of patients with pancreatic infection have a raised white cell count, many with uncomplicated acute pancreatitis also develop leucocytosis[103,104]. Furthermore, in some patients with pancreatic infection the white cell count is normal or decreased[45,60]. Blood cultures are unhelpful in making a diagnosis of pancreatic infection. They are rarely positive because bacteraemia from an abscess tends to be intermittent and transient[36,43,48,52,54,63,105,106]. Furthermore, bacteraemia may arise from other sites, such as an infected urinary or respiratory tract (*Table 3*)[105], both of which are not infrequent in sick patients with acute pancreatitis[70,104]. Nevertheless, among patients with severe necrotizing pancreatitis, positive blood cultures are associated with an increased mortality rate[106].

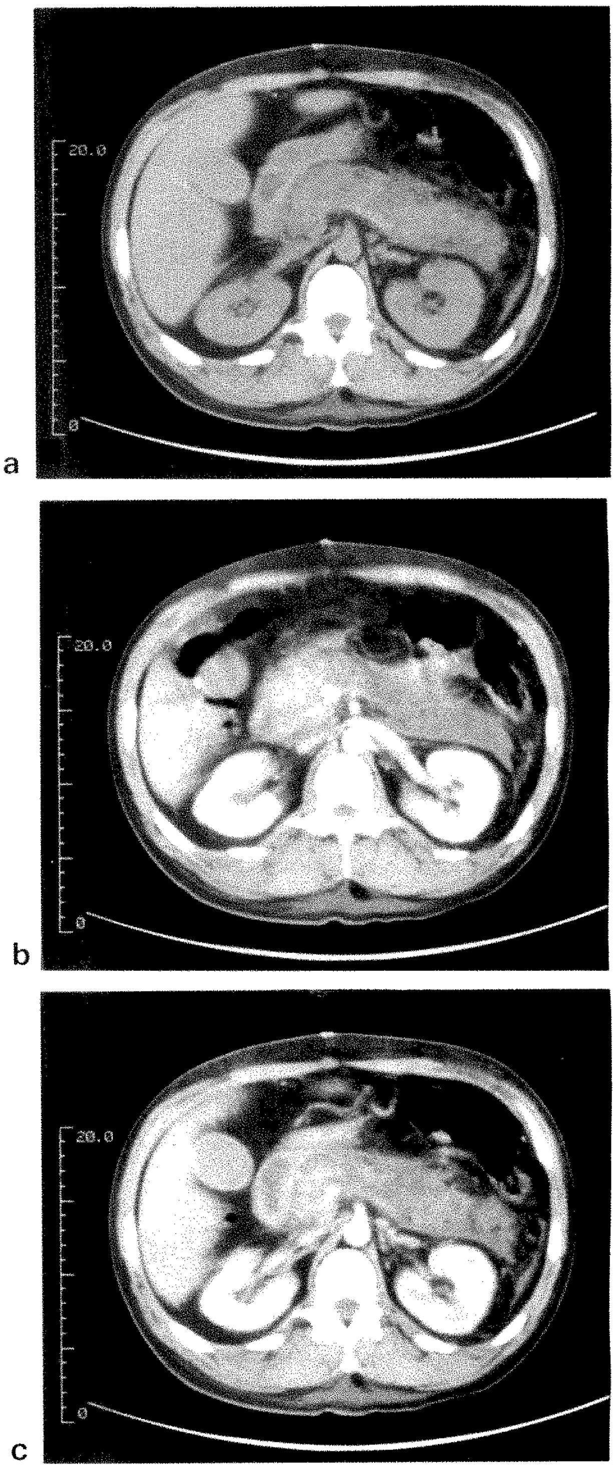

Figure 1 *Computed tomography of the pancreas in a patient with severe acute pancreatitis.* **a** *Without contrast;* **b** *contrast enhancement demonstrating 50 per cent necrosis;* **c** *contrast enhancement demonstrating 80 per cent necrosis*

Although prognostic scoring systems do not correlate well with necrosis or septic complications, patients with pancreatic infection have higher Ranson and APACHE scores than those with sterile acute pancreatitis[23,25,27,33,38]. However, approximately 10 per cent of pancreatic infections occur in patients with a Ranson score[38] <2 and an APACHE II score[25] <10. Other measures that indicate pancreatic necrosis, an important factor in the development of infection[103,104], include serum levels of C-reactive protein, α_1 protease inhibitor, α_2 macroglobulin, C3 and C4 complement and poly-[C]-specific ribonuclease[23,107–110]. However, there is little evidence that any of these predicts pancreatic sepsis[111–114]. The non-specific nature of the clinical features and absence of reliable laboratory indicators of sepsis mean that a high index of suspicion is insufficient to make the diagnosis: further investigations are required[24].

Table 3 *Sources of bacteraemia*

Source	Positive blood culture (%)
Respiratory tract	17
Genitourinary tract	17
Abscess	8
Surgical wound	4
Biliary tract	3
Gastrointestinal tract	3
Skin	3
Intravenous catheter	3
Urethral catheter	2
Uncertain	36

All patients with moderate or severe ('poor prognosis') acute pancreatitis should undergo contrast-enhanced computed tomography (CT)[19,24,25,27,38,46,104,115–121]. If this is not available patients should be referred to centres with the necessary services and expertise in this field. Early CT (within

3 days) is recommended because it identifies patients at increased risk of developing pancreatic infection[25,27,38,122,123]. Pancreatic necrosis may be revealed by areas of hypoperfusion (parenchymal enhancement after intravenous contrast <40 Hounsfield units[120]), or alternatively a fluid collection or abscess may be demonstrated (*Figure 1*). The extent of necrosis is estimated from the ratio of the area of decreased enhancement to the area of normal perfusion (parenchymal enhancement >50 Hounsfield units[120])[27]. This correlates well with the extent of necrosis at operation[121].

Pancreatic necrosis is identified by contrast-enhanced CT in 17–20 per cent of patients with acute pancreatitis[21,122]. Necrosis or an abscess is demonstrated in >80 per cent and has a false-negative rate of only 3 per cent[21,24,31,36,37,39,43,45,46,49,50,52–54,56–60,62–66]. The area of pancreatic necrosis in patients with pancreatic infection is greater than that in those without infection[27,33]. Patients with >50 per cent pancreatic necrosis have a 25–50 per cent chance of infection[24,66].

Although CT is extremely useful, in most patients pancreatic necrosis is sterile; a pancreatic or peripancreatic fluid collection may represent a pseudocyst, old haemorrhage or a sterile collection rather than an abscess[124]. Therefore, the diagnosis of pancreatic infection can be made with confidence only if bacteria are demonstrated.

Microscopy and culture of fine-needle aspirates reliably distinguish between sterile and infected tissue[104,119,125]. Aspirations are performed from areas of hypoperfusion or fluid collections shown by contrast-enhanced CT. It is important to ensure the fine needle (20–22 G) is inserted using an aseptic technique along a route that avoids the bowel. The aspirated sample is immediately Gram stained and aerobic and anaerobic cultures obtained. In experienced hands it is a safe investigation; false-positive and false-negative results are infrequent[23,46,47,66,80,104,119,124,125]. The early diagnosis of pancreatic infection might be achieved if pancreatic necrosis or fluid collections seen by CT were sampled and the aspirate cultured and examined microscopically. Most of the CT changes associated with patients at risk of developing pancreatic infection are manifest early (within 3 days)[38,122]. However, fluid accumulation and/or necrosis, or infection of sterile necrosis, may develop later. Serial CT and fine-needle aspiration microbiology of areas of necrosis and fluid collections will identify these patients and monitor progress[25,66,125,126].

Treatment

Treatment depends on making an accurate diagnosis. Fluid collections and acute pseudocysts whether infected or not may be treated by percutaneous drainage[17–19,118,126–130]. However, when complications develop, such as rupture, haemorrhage, biliary or gastric outlet obstruction, surgery may be required as an emergency. In these patients the wall of the pseudocyst is frequently too immature for internal drainage via a cystogastrostomy or cystojejunostomy, and external drainage is appropriate.

The treatment of most pancreatic abscesses is surgical. Necrotic tissue and multiple or multilocular abscesses prevent adequate drainage through even large-bore catheters[41,47,66,126]. However, percutaneous drainage may be successfully employed in a few carefully selected patients with unilocular collections in the absence of pancreatic necrosis or severe disease[126,130]. The role of percutaneous drainage as a temporary measure in the critically ill patient is controversial. In some patients it provides temporary relief before surgery[30,41,118,126], whereas in others it makes no difference and may delay appropriate surgical treatment[23,126,130].

As with pancreatic abscesses there is general agreement that infected pancreatic necrosis is an absolute indication for surgery[17,27,29,51,81,131]; non-operative or percutaneous management is usually associated with a fatal outcome[15,50,126,130,132]. However, when the diagnosis is uncertain or necrosis sterile, treatment is controversial.

The postoperative mortality rate for patients operated on for sterile necrotizing pancreatitis is approximately 17 per cent[20,23,28,30,31,33,34]. Postoperative sepsis is the principal cause of death among these patients; approximately 20 per cent develop sepsis, with a mortality rate of about 60 per cent, while the remaining 80 per cent have a mortality rate of 7 per cent. An alternative is to manage patients with sterile pancreatic necrosis conservatively[27,35,78,123,133–136]. Buchler *et al.* reported a 13 per cent mortality rate in patients with necrotizing pancreatitis who responded and 8 per cent among those in whom conservative treatment failed[123]. Similarly, in the series reported by Bradley and Allen, all patients with sterile pancreatic necrosis were managed conservatively, with no deaths[27]. However, these excellent results were achieved in centres with a particular interest in the disease and were dependent on infection being excluded with confidence. CT and fine-needle aspiration microbiology can generally achieve this.

Surgical methods

The fundamental principle underlying surgical treatment of pancreatic infection is thorough debridement of devitalized tissue with drainage of fluid collections. Conventionally, the abdomen is closed primarily with dependent drainage or sump suction[20,21,25,43,45,46,48,51,55]. In many patients this is sufficient to abort the infected inflammatory process. However, in about 30 per cent persisting inflammation with residual or recurrent infection necessitates further surgical intervention which is associated with very high rates of morbidity and mortality[77]. For this reason a number of groups advocate necrosectomy and continuous closed postoperative lavage of the lesser sac and infected areas through drainage catheters positioned at the first operation[136–140]. In patients with infected necrosis the mortality rate is reduced to about 15 per cent. However, the reoperation rate is still high at about 20 per cent.

Alternatively, the abdomen can be 'left open' for planned relaparotomies[29,40,54,63]. Patients with extensive areas of infected necrotic tissue, large multiloculated or multiple abscesses, or persisting haemorrhage are particularly suited to open drainage and packing[25]. The operative technique is the same except that, after abscess drainage and debridement of devitalized tissue, the lesser sac is packed. The laparotomy wound is then loosely closed. Planned reoperation under general anaesthesia is performed every 36–48 h. The packs are carefully removed and further debridement performed if necessary. This is repeated until healthy granulation tissue appears and dressings can be changed in the intensive care unit. The mortality rate after open drainage is similar to that reported for local lavage, but the morbidity rate may be greater. However, it must be stressed that no prospective trial has been published.

The overall postoperative mortality rate after drainage of pancreatic abscesses is about 30 per cent, but this has been declining in recent years[77]. Surgical debridement of infected pancreatic necrosis is associated with a 40 per cent mortality rate[20,29,30,81]. However, these results were among severely ill patients with sepsis, in whom the diagnosis had usually been made on clinical grounds. In centres with a special expertise in treating patients with acute pancreatitis, increasing use of CT and fine-needle aspiration microbiology appears to be improving diagnostic accuracy and allowing earlier diagnosis and treatment. With such a policy, the mortality rate among patients with infected pancreatic necrosis has fallen to <20 per cent[23,25,27].

Antimicrobial treatment

Currently there is no clinical evidence that antimicrobial agents are effective in either preventing or treating pancreatic infection. Many series have been reported in which pancreatic infection developed despite continuous administration of antimicrobials from the time of admission to hospital[14,141–144]. In addition, prior antimicrobial therapy does not render samples taken by percutaneous fine-needle aspiration sterile[119]. To date, only three prospective clinical trials have been performed to evaluate the role of prophylactic antimicrobial treatment[145-147]. However, these trials were inconclusive: too few patients were enrolled, inappropriate antimicrobials were used, and all patients, even those with very mild acute pancreatitis, were included. Most patients with acute pancreatitis have mild acute oedematous disease in which the risk of developing pancreatic infection is low. Thus, including all patients in such studies must inevitably dilute the effects of prophylactic antimicrobials in the severe necrotizing form.

Ampicillin, the antimicrobial used in these studies, was an unsuitable choice because it is ineffective against most pancreatic pathogens and does not reach therapeutic levels in the gland[14,148]. The aminoglycosides, some cephalosporins and tetracyclines also have limited penetration[14,148], suggesting that there may be a blood–pancreas barrier[149].

Antimicrobials that do reach therapeutic levels in the pancreas include cefotaxime, ceftazidime, clindamycin, ciprofloxacin, rifampicin, trimethoprim–sulphamethoxazole and metronidazole[14,148]. Since most pancreatic infections are caused by Gram-negative enteric aerobes[77], the antimicrobials most likely to be effective in the prevention or treatment of pancreatic infection are ciprofloxacin, cefotaxime or ceftazidime. Indeed, in an animal model of pancreatic infection in acute pancreatitis, early treatment with cefotaxime was effective[90].

Antimicrobial drugs have well recognized side-effects and alter intestinal microbial flora, predisposing to the translocation of bacteria. Their use should be limited until their efficacy is proven. At present, antimicrobials should be prescribed only for the treatment of proven infection, as prophylaxis to prevent bacteraemia, and for patients undergoing surgery. There is currently no evidence that they are of benefit in patients with uncomplicated acute pancreatitis.

Conclusions

Fewer patients now die from either cardiopulmonary or renal complications of acute pancreatitis, largely as a result of improved medical measures. There is now scope for improvement in the outcome of septic complications with early surgical intervention and judicious use of appropriate antimicrobials. Patients with septic complications should be managed in centres with the necessary technology and expertise.

An invasive and aggressive approach to the management of all patients with severe acute pancreatitis is suggested. Once patients are identified as having moderate or severe (poor prognosis) pancreatitis, contrast-enhanced CT should be performed. Fine-needle aspiration microbiology of areas of necrosis or fluid collections will ensure early detection of infection, allowing treatment to be instituted before established sepsis leads to further deterioration. In contrast, patients with sterile pancreatic necrosis may be carefully observed. Serial CT and aspiration microbiology are required if the clinical condition does not improve.

Surgical intervention is indicated in most patients with documented pancreatic infection or with clinical deterioration with suspected infection, and for those who fail to improve or who deteriorate despite intensive medical measures. The aims of surgery are to drain fluid collections and debride all necrotic tissue. In most patients, primary closure with continuous postoperative lavage of the lesser sac is successful. In patients with extensive necrosis 'open drainage' with planned reoperations may be preferable.

References

1. Corfield AP, Cooper MJ, Williamson RCN. Acute pancreatitis: a lethal disease of increasing incidence. *Gut* 1985; **26**: 724–9.
2. Bourke JB. Variation in annual incidence of primary acute pancreatitis in Nottingham, 1969–1974. *Lancet* 1975; **ii**: 967–9.
3. McMahon MJ. Incidence and mortality of acute pancreatitis. *BMJ* 1977; **ii**: 1350 (Letter).
4. Graham DF. Incidence and mortality of acute pancreatitis. *BMJ* 1977; **ii**: 1603.
5. Trapnell JE, Duncan EHL. Patterns of incidence in acute pancreatitis. *BMJ* 1975; **ii**: 179–83.
6. Wilson C, Imrie CW. Changing patterns of incidence and mortality from acute pancreatitis in Scotland, 1961–1985. *Br J Surg* 1990; **77**: 731–4.
7. Imrie CW. The aetiology of acute pancreatitis. In: Gyr KE, Singer MV, Sarles H, eds. *Pancreatitis – Concepts and Classification*. Amsterdam: Elsevier Science Publishers, 1984: 339–43.
8. Cuschieri A, Wood RAB, Cumming JRG, Meehan SE, Mackie CR. Treatment of acute pancreatitis with fresh frozen plasma. *Br J Surg* 1983; **70**: 710–12.
9. Williamson RCN. Early assessment of severity in acute pancreatitis. *Gut* 1984; **25**: 1331–9.
10. Frey CF, Bradley EL, Beger HG. Progress in acute pancreatitis. *Surg Gynecol Obstet* 1988; **167**: 282–6.
11. Aldridge MC, Ornstein M, Glazer G, Dudley HAF. Pancreatic resection for severe acute pancreatitis. *Br J Surg* 1985; **72**: 796–800.
12. Beger HG, Buchler M, eds. *Acute Pancreatitis*. Berlin: Springer-Verlag, 1987.
13. Kune GA, Brough W. Surgical intervention in severe acute pancreatitis: 476 cases in 20 years. *Ann R Coll Surg Engl* 1989; **71**: 23–7.
14. Bradley EL. Antibiotics in acute pancreatitis: current status and future direction. *Am J Surg* 1989; **158**: 472–6.
15. Buggy BP, Nostrant TT. Lethal pancreatitis. *Am J Gastroenterol* 1983; **78**: 810–14.
16. Ranson JHC, Spencer FC. Prevention, diagnosis, and treatment of pancreatic abscess. *Surgery* 1977; **82**: 99–106.
17. Gerzof SG, Banks PA, Spechler SJ *et al.* Role of guided percutaneous aspiration in early diagnosis of pancreatic sepsis. *Dig Dis Sci* 1984; **29**: 950.
18. Imrie CW, Buist LJ, Shearer MG. Importance of cause in the outcome of pancreatic pseudocysts. *Am J Surg* 1988; **156**: 159–62.
19. Mainwaring R, Kern J, Schenk WG, Rudolf L. Differentiating pancreatic pseudocyst and pancreatic necrosis using computerized tomography. *Ann Surg* 1989; **209**: 562–8.
20. Wilson C, McArdle CS, Carter DC, Imrie CW. Surgical treatment of acute necrotizing pancreatitis. *Br J Surg* 1988; **75**: 1119–23.
21. Allardyce DB. Incidence of necrotizing pancreatitis and factors related to mortality. *Am J Surg* 1987; **154**: 295–9.
22. Pederzoli P, Bassi C, Vesentini S *et al.* Retroperitoneal and peritoneal drainage and lavage in the treatment of severe necrotizing pancreatitis. *Surg Gynecol Obstet* 1990; **170**: 197–203.
23. Rattner DW, Legermate DA, Lee MJ, Mueller PR, Warshaw AL. Early surgical debridement of symptomatic pancreatic necrosis is beneficial irrespective of infection. *Am J Surg* 1991; **163**: 105–10.
24. Block S, Maier W, Bittner R, Buchler M, Malfertheiner P, Beger HG. Identification of pancreas necrosis in severe acute pancreatitis: imaging procedures *versus* clinical staging. *Gut* 1986; **27**: 1035–42.
25. Stanten R, Frey CF. Comprehensive management of acute necrotizing pancreatitis and pancreatic abscess. *Arch Surg* 1990; **125**: 1269–75.
26. Kivilaakso E, Fraki O, Nikki P, Lempinen M. Resection of the pancreas for acute fulminant pancreatitis. *Surg Gynecol Obstet* 1981; **152**: 493–8.
27. Bradley EL, Allen K. A prospective longitudinal study of observation *versus* surgical intervention in the management of necrotizing pancreatitis. *Am J Surg* 1991; **161**: 19–25.
28. Smadja C, Bismuth H. Pancreatic debridement for acute necrotizing pancreatitis: an obsolete procedure? *Br J Surg* 1986; **73**: 408–10.
29. Bradley EL. Management of infected pancreatic necrosis by open drainage. *Ann Surg* 1987; **206**: 542–50.
30. Warshaw AL, Imbembo AL, Civetta JM, Daggett WM. Surgical intervention in acute necrotizing pancreatitis. *Am J Surg* 1974; **127**: 484–91.
31. Wertheimer MD, Norris CS. Surgical management of necrotizing pancreatitis. *Arch Surg* 1986; **121**: 484–7.
32. Frey CF, Lindenauer SM, Miller TA. Pancreatic abscesses. *Surg Gynecol Obstet* 1979; **149**: 722–6.
33. Roscher R, Beger HG. Bacterial infection of pancreatic necrosis. In: Beger HG, Buchler M, eds. *Acute Pancreatitis*. Berlin:

Springer-Verlag, 1987: 314–17.
34. Lawson DW, Daggett WM, Civetta JM, Corry RJ, Bartlett MK. Surgical treatment of acute necrotizing pancreatitis. *Ann Surg* 1970; **172**: 605–17.
35. Banks PA, Gerzof SG, Chong FK *et al.* Bacteriological status of necrotic tissue in necrotizing pancreatitis. *Pancreas* 1990; **5**: 330–3.
36. Altemeier WA, Alexander JW. Pancreatic abscesses. *Arch Surg* 1963; **87**: 80–9.
37. Bittner R, Block S, Buchler M, Beger HG. Pancreatic abscess and infected pancreatic necrosis. Different local septic complications in acute pancreatitis. *Dig Dis Sci* 1987; **32**: 1082–7.
38. Ranson JHC, Balthazar E, Caccavale R, Cooper M. Computed tomography and the prediction of pancreatic abscess in acute pancreatitis. *Ann Surg* 1985; **201**: 656–65.
39. Miller TA, Lindenauer SM, Frey CF, Stanley JC, Arbor A. Pancreatic abscess. *Arch Surg* 1974; **108**: 545–51.
40. Pemberton JH, Becker JM, Dozois RR, Nagorney DM, Ilstrup D, Remine WH. Controlled open lesser sac drainage for pancreatic abscess. *Ann Surg* 1986; **203**: 600–4.
41. Karlson EC, Martin C, Fankuchen SI, Mattern RF, Schultz RW, Casarella WJ. Percutaneous drainage of pancreatic pseudocysts and abscesses. *Radiology* 1981; **142**: 619–24.
42. Hurley JE, Vargish T. Early diagnosis and outcome of pancreatic abscesses in pancreatitis. *Am Surg* 1987; **53**: 29–33.
43. Malangoni MA, Shallcross JC, Seiler JG, Richardson JD, Polk HC. Factors contributing to fatal outcome after treatment of pancreatic abscesses. *Ann Surg* 1986; **203**: 605–13.
44. McClave SA, McAllister EW, Karl RC, Nord HJ. Pancreatic abscess: 10-year experience at the University of South Florida. *Am J Gastroenterol* 1986; **81**: 180–4.
45. Warshaw AL, Jin G. Improved survival in 45 patients with pancreatic abscess. *Ann Surg* 1985; **202**: 408–17.
46. Crass RA, Meyer AA, Jeffrey RB *et al.* Pancreatic abscess: impact of computerized tomography on early diagnosis and surgery. *Am J Surg* 1985; **150**: 127–31.
47. Sostre CF, Flournoy JG, Bova JG, Goldstein HM, Schenker S. Pancreatic phlegmon. *Dig Dis Sci* 1985; **30**: 918–27.
48. Kaushik SP, Vohra R, Verma S, Sabharwal A. Pancreatic abscess: a review of 17 cases. *Br J Surg* 1984; **71**: 141–3.
49. Shi ECP, Yeo BW, Ham JM. Pancreatic abscesses. *Br J Surg* 1984; **71**: 689–91.
50. Bradley EL, Fulenwider JT. Open treatment of pancreatic abscess. *Surg Gynecol Obstet* 1984; **159**: 509–13.
51. Aranha GV, Prinz RA, Greenlee HB. Pancreatic abscess: an unresolved surgical problem. *Am J Surg* 1982; **144**: 543–8.
52. Watters JM, Mullens JE. Pancreatic abscesses. *Can J Surg* 1982; **25**: 460–2.
53. Saxon A, Reynolds JT, Doolas A. Management of pancreatic abscesses. *Ann Surg* 1981; **194**: 545–52.
54. Davidson ED, Bradley EL. 'Marsupialization' in the treatment of pancreatic abscess. *Surgery* 1981; **89**: 252–6.
55. Chang FC, Van Houden CE. Debridement pancreatectomy for pancreatic abscess. *Am J Surg* 1981; **142**: 664–6.
56. Berne TV, Donovan AJ. Synchronous anterior celiotomy and posterior drainage of pancreatic abscess. *Arch Surg* 1981; **116**: 527–33.
57. Donahue PE, Nyhus LM, Baker RJ. Pancreatic abscess after alcoholic pancreatitis. *Arch Surg* 1980; **115**: 905–9.
58. Paloyan D, Simonowitz D, Bates RJ. Guidelines on the management of patients with pancreatic abscess. *Am J Gastroenterol* 1978; **69**: 97–100.
59. Owens BJ, Hamit HF. Pancreatic abscess and pseudocyst. *Arch Surg* 1977; **112**: 42–5.
60. Holden JL, Berne TV, Rosoff L. Pancreatic abscess following acute pancreatitis. *Arch Surg* 1976; **111**: 858–61.
61. Camer SJ, Tan EGC, Warren KW, Braasch JW. Pancreatic abscess. A critical analysis of 113 cases. *Am J Surg* 1975; **129**: 426–31.
62. Dencker H, Liedberg G, Tibblin S. Surgical aspects of pancreatic abscess. *Acta Chirurgica Scandinavica* 1972; **138**: 609.
63. Bolooki H, Jaffe B, Gliedman ML. Pancreatic abscesses and lesser omental sac collections. *Surg Gynecol Obstet* 1968; **126**: 1301–8.
64. Steedman RA, Doering R, Carter R. Surgical aspects of pancreatic abscess. *Surg Gynecol Obstet* 1967; **125**: 757–62.
65. Farringer JL, Robbins LB, Pickens DR. Abscesses of the pancreas. *Surgery* 1966; **60**: 964–70.
66. Fink AS, Hiatt JR, Pitt HA *et al.* Indolent presentation of pancreatic abscess. Experience with 100 cases. *Arch Surg* 1988; **123**: 1067–72.
67. Kune GA, King R. Late complications of acute pancreatitis: pancreatic swelling, cyst and abscess. *Med J Aust* 1973; **1**: 1241–6.
68. Evans FC. Pancreatic abscess. *Am J Surg* 1969; **117**: 537–40.
69. Howard JM. Pancreatitis. In: Howard JM, Jordan GL, eds. *Surgical Diseases of the Pancreas.* Philadelphia, Pennsylvania: JB Lippincott, 1960: 92–202.
70. Grace SG, State D. Septic complications of pancreatitis. *Br J Surg* 1976; **63**: 229–32.
71. Ranson JHC. Acute pancreatitis. *Curr Probl Surg* 1979; **16**: 1–84.
72. Cruickshank AH. *Pathology of the Pancreas.* Berlin: Springer-Verlag, 1986.
73. Blumenthal HT, Probstein JG. *Pancreatitis.* New York: Charles Thomas, 1959.
74. Gambill EE. *Pancreatitis.* St Louis, Missouri: Mosby, 1973.
75. Elman R. Acute interstitial pancreatitis. *Surg Gynecol Obstet* 1933; **57**: 291–309.
76. Fitz RH. Acute pancreatitis. *Boston Medical and Surgical Journal* 1889; **120**: 229–35.
77. Widdison AL, Alvarez C, Reber HA. Surgical intervention in acute pancreatitis: when and how. *Pancreas* 1991; **6**: S44–51.
78. Bradley EL. Operative management of acute pancreatitis: ventral open packing. *Hepatogastroenterology* 1991; **38**: 134–8.
79. Hancke E, Marklein G. Bacterial contamination of the pancreas with intestinal germs: a cause of acute suppurative pancreatitis? In: Beger HG, Buchler M, eds. *Acute Pancreatitis.* Berlin: Springer-Verlag, 1987: 87–9.
80. Warshaw AL. Pancreatic abscesses. *N Engl J Med* 1972; **287**: 1234–6.
81. Beger HG, Bittner R, Block S, Buchler M. Bacterial contamination of pancreatic necrosis: a prospective clinical study. *Gastroenterology* 1986; **91**: 433–8.
82. Simmons RL, Howard RJ. *Surgical Infectious Diseases.* New York: Appleton–Century–Crofts, 1982.
83. Weinstein MP, Reller LB, Murphy JR. Clinical importance of polymicrobial bacteremia. *Diagn Microbiol Infect Dis* 1986; **5**: 185–96.
84. Thompson JE, Tompkins RK, Longmire WP. Factors in the management of acute cholangitis. *Ann Surg* 1982; **195**: 137–45.
85. Keighley MRB. Infection and the biliary tree. In: Blumgart LH, ed. *The Biliary Tract. Clinical Surgery International.* Vol. 5. London: Churchill Livingstone, 1982: 219–35.
86. Widdison AL, Karanjia ND, Alvarez C, Reber HA. Sources of pancreatic pathogens in acute necrotizing pancreatitis. *Gastroenterology* 1991; **100**: A304.
87. Widdison AL, Karanjia ND, Reber HA. Route(s) of spread of bacteria to the pancreas in acute necrotizing pancreatitis. *Pancreas* 1990; **5**: 736.
88. Tarpila E, Nystrom P-O, Franzen L, Lilja I, Ihse I. Acute experimental suppurative pancreatitis in the rat. *Acta Chirurgica Scandinavica* 1988; **154**: 379–83.
89. Semsch B, Heitz G, Berger G, Haring R. Influence of *E. coli* on the course of acute pancreatitis in mini-pigs. In: Beger HG, Buchler M, eds. *Acute Pancreatitis.* Berlin: Springer-Verlag, 1987: 90–9.
90. Widdison AL, Karanjia ND, Reber HA. The outcome of pancreatic colonization in acute necrotizing pancreatitis and the efficacy of cefotaxime treatment. *Pancreas* 1990; **5**: 736.
91. Widdison AL, Karanjia ND, Alvarez C, Reber HA. The association between pancreatic infection and the severity of acute pancreatitis. *Gastroenterology* 1991; **100**: A304.
92. Adham NF, Song MK, Haberfelde GC. Relationship between the functional status of the reticuloendothelial system and the outcome of experimentally induced pancreatitis in young mice. *Gastroenterology* 1983; **84**: 461–9.
93. Widdison AL, Karanjia ND, Alvarez C, Reber HA. Reticuloendothelial system function, and the influence of levamisole on the development of pancreatic infection in acute necrotizing pancreatitis. *Am J Surg* 1992; **163**: 100–4.
94. Curley PJ, Lancaster F, McMahon MJ, Boylston A. Evaluation of the immune system in acute pancreatitis. *Pancreas Club Abstracts* 1991; **25**: 42.
95. Scott-Conner CEH, Grogan JB, Scher KS, Bernstein J. Impaired clearance of *Escherichia coli* bacteremia in early biliary obstruction. *Am J Surg* 1989; **157**: 210–14.
96. Sjolund B, Lasson A, Ohlsson K. The elimination of trypsin–α-macroglobulin complexes from the blood circulation in pigs during acute pancreatitis and after massive intravenous trypsin infusion. *Scand J Clin Lab Invest* 1987; **47**: 131–41.

97. Ohlsson K, Laurell C-B. The disappearance of enzyme–inhibitor complexes from the circulation of man. *Clin Sci Mol Med* 1976; **51**: 87–92.
98. Browder W, Williams D, Pretus H *et al.* Beneficial effect of enhanced macrophage function in the trauma patient. *Ann Surg* 1990; **211**: 605–13.
99. Alexander JW. Emerging concepts in the control of surgical infections. *Surgery* 1974; **75**: 934–46.
100. Alexander JW, Meakins JL. A physiological basis for the development of opportunistic infections in man. *Ann Surg* 1972; **176**: 273–87.
101. Saba TM. Reticuloendothelial defense: its relevance to cardiopulmonary function in septic surgical, trauma and burn patients. *Contemporary Surgery* 1979; **14**: 64–78.
102. Mason HDW, Forgash A, Balch HH. Intestinal fistula complicating pancreatic abscess. *Surg Gynecol Obstet* 1975; **140**: 39–43.
103. Banks PA, Gerzof SG, Robbins AH *et al.* Diagnosis of pancreatic infection by CT guided aspiration: an update. *Pancreas* 1988; **3**: 590.
104. Gerzof SG, Banks PA, Robbins AH *et al.* Early diagnosis of pancreatic infection by computed tomography guided aspiration. *Gastroenterology* 1987; **93**: 1315–20.
105. Kreger BE, Craven DE, Carling PC, McCabe WR. Gram negative bacteremia. III. Reassessment of etiology, epidemiology and ecology in 612 patients. *Am J Med* 1980; **68**: 332–44.
106. Fugger R, Schulz F, Rogy M, Herbst F, Mirza D, Fritsch A. Open approach in pancreatic and infected pancreatic necrosis: laparostomies and preplanned revisions. *World J Surg* 1991; **15**: 516–21.
107. McMahon MJ, Bower M, Mayer AD, Cooper EH. Relation of alpha-2 macroglobulin and other antiproteases to the clinical features of acute pancreatitis. *Am J Surg* 1984; **147**: 164–9.
108. Aldridge MC. Diagnosis of pancreatic necrosis. *Br J Surg* 1988; **75**: 99–100.
109. Buchler M, Uhl W, Malfertheiner P. Biochemical staging of acute pancreatitis. In: Beger HG, Buchler M, eds. *Acute Pancreatitis.* New York: Springer-Verlag, 1987: 143–53.
110. Buchler M, Malfertheiner P, Schoetensack C, Uhl W, Beger HG. Sensitivity of antiproteases, complement factors and C-reactive protein in detecting pancreatic necrosis. Results of a prospective clinical trial. *Int J Pancreatol* 1986; **1**: 227–35.
111. Banks PA. Sepsis indicators in acute pancreatitis. *Pancreas* 1987; **2**: 497–8.
112. Block S, Bittner R, Beger HG. Sepsis indicators in acute pancreatitis. In: Beger HG, Buchler M, eds. *Acute Pancreatitis.* Berlin: Springer-Verlag, 1987: 164–70.
113. Buchler M. Objectification of the severity of acute pancreatitis. *Hepatogastroenterology* 1991; **38**: 101–8.
114. Fagniez PL, Rotman N, Pezet D, Cherqui D, Mathieu D. Severe acute pancreatitis: new insights in diagnosis and management. *Dig Dis* 1991; **9**: 165–78.
115. Hill MC, Huntington DK. CT and acute pancreatitis. *Gastroenterol Clin North Am* 1990; **19**: 811–42.
116. Federle MP, Jeffrey RB, Crass RA, Van Dalsem V. Computed tomography of pancreatic abscesses. *Am J Radiol* 1981; **136**: 879–82.
117. London NJM, Leese T, Lavelle JM *et al.* Rapid-bolus contrast-enhanced dynamic computed tomography in acute pancreatitis: a prospective study. *Br J Surg* 1991; **78**: 1452–6.
118. Freeny PC, Lewis GP, Traverso LW, Ryan JA. Infected pancreatic fluid collections: percutaneous catheter drainage. *Radiology* 1988; **167**: 435–44.
119. Banks PA. Infected necrosis: morbidity and therapeutic consequences. *Hepatogastroenterology* 1991; **38**: 116–19.
120. Bradley EL, Murphy F, Ferguson C. Prediction of pancreatic necrosis by dynamic pancreatography. *Ann Surg* 1989; **210**: 495–505.
121. Maier W. Early objective diagnosis and staging of acute pancreatitis by contrast enhanced computed tomography. In: Beger HG, Buchler M, eds. *Acute Pancreatitis.* Berlin: Springer-Verlag, 1987: 132–40.
122. Balthazar EJ, Robinson DL, Megibow AJ. Acute pancreatitis: value of CT in establishing prognosis. *Radiology* 1990; **174**: 331–6.
123. Buchler M, Malfertheiner P, Uhl W, Beger HG. Conservative treatment of necrotizing pancreatitis in patients with minor pancreatic necrosis. *Pancreas* 1988; **3**: 592.
124. Hill MC, Dach JL, Barkin J, Isikoff MB, Morse B. The role of percutaneous aspiration in the diagnosis of pancreatic abscess. *Am J Radiol* 1983; **141**: 1035–8.
125. Barkin JS, Pereiras R, Hill M, Levi J, Isikoff M, Rogers AI. Diagnosis of pancreatic abscess via percutaneous aspiration. *Dig Dis Sci* 1982; **27**: 1011–14.
126. Steiner E, Mueller PR, Hahn PF *et al.* Complicated pancreatic abscesses: problems in interventional management. *Radiology* 1988; **167**: 443–6.
127. Gerzof SG, Johnson WC, Robbins AH, Spechler SJ, Nabseth DC. Percutaneous drainage of infected pancreatic pseudocysts. *Arch Surg* 1984; **119**: 888–93.
128. Banks PA, Gerzof SG. Pancreatic pseudocyst and abscess – is percutaneous drainage a reasonable option? In: Barkin JS, Rogers MD, eds. *Difficult Decisions in Digestive Diseases.* Chicago, Illinois: Year Book Medical, 1989: 181–91.
129. Brown CD, Adams WE, Wheeler WG, Jones MJ. Diagnosis and treatment of intra-abdominal fluid collections. *J Ky Med Assoc* 1987; **85**: 69–74.
130. Adams DB, Harvey TS, Anderson MC. Percutaneous catheter drainage of infected pancreatic and peri-pancreatic fluid collections. *Arch Surg* 1990; **125**: 1554–7.
131. Hiatt JR, Fink AS, King W, Pitt HA. Percutaneous aspiration of peripancreatic fluid collections: a safe and effective diagnostic procedure. *Dig Dis Sci* 1985; **30**: 974–7.
132. Renner IG, Savage WT, Pantoja JL, Renner VJ. Death due to acute pancreatitis: a retrospective analysis of 405 autopsy cases. *Dig Dis Sci* 1985; **30**: 1005–18.
133. Nordback I, Pessi T, Auvinen O, Autio V. Determination of necrosis in necrotizing pancreatitis. *Br J Surg* 1985; **7**: 284–6.
134. Reber HA. Surgical intervention in necrotizing pancreatitis. *Gastroenterology* 1986; **91**: 433.
135. Ranson JHC, Rifkind KM, Rases DF, Fink SD, Eng K, Spencer FC. Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet* 1974; **139**: 69–81.
136. Larvin M, Chalmers AG, Robinson PJ, McMahon MJ. Debridement and closed cavity irrigation for the treatment of pancreatic necrosis. *Br J Surg* 1989; **76**: 465–71.
137. Bassi C, Vesentini S, Nifippo F *et al.* Pancreatic abscesses and other pus harboring collections related to pancreatitis: a review of 108 cases. *World J Surg* 1990; **14**: 505–12.
138. Beger HG, Buchler M, Bittner R, Nevelainen T, Roscher R. Necrosectomy and postoperative local lavage in necrotizing pancreatitis. *Br J Surg* 1988; **75**: 207–12.
139. Gebhardt C, Gall FP. Importance of peritoneal irrigation after surgical treatment of hemorrhagic, necrotizing pancreatitis. *World J Surg* 1981; **5**: 379–85.
140. Nicholson ML, Mortensen NJ, Espiner HJ. Pancreatic abscess: results of prolonged irrigation of the pancreatic bed after surgery. *Br J Surg* 1988; **75**: 88–91.
141. Trudel JL, Thompson AG, Brown RA. Prophylactic use of antibiotics in pancreatic sepsis: 25 year reappraisal. *Can J Surg* 1984; **27**: 567–70.
142. Lankisch PG, Klesel N, Seeger K, Siedel G, Winckler K. Penetration of cefotaxime into the pancreas. *Z Gastroenterol* 1983; **21**: 601–3.
143. Cameron JL, Howes R, Zuidema GD. Antibiotic therapy in acute pancreatitis. *Surg Clin North Am* 1975; **55**: 1319–24.
144. Kodesch R, DuPont HL. Infectious complications of acute pancreatitis. *Surg Gynecol Obstet* 1973; **136**: 763–8.
145. Finch WT, Sawyers JL, Schenker S. A prospective study to determine the efficacy of antibiotics in acute pancreatitis. *Ann Surg* 1976; **183**: 667–71.
146. Howes R, Zuidema GD, Cameron JL. Evaluation of prophylactic antibiotics in acute pancreatitis. *J Surg Res* 1975; **18**: 197–200.
147. Craig RM, Dordel E, Myles L. The use of ampicillin in acute pancreatitis. *Ann Intern Med* 1975; **83**: 831–2.
148. Buchler M, Malfertheiner P, Frieb H *et al.* The penetration of antibiotics into human pancreas. *Infection* 1989; **17**: 20–5.
149. Burns GP, Stein TA, Kabnick LS. Blood–pancreatic juice barrier to antibiotic excretion. *Am J Surg* 1986; **151**: 205–8.

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Interleukin 2 therapy: current role in surgical oncological practice

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The use of recombinant interleukin 2 (rIL-2) in clinical practice has opened up new and beneficial avenues in the treatment of certain malignant diseases. Although rIL-2 can stimulate a range of host antitumour defence mechanisms, only 30–40 per cent of patients who are treated will respond to such therapy as assessed by a reduction in tumour volume. The effect of rIL-2-based treatment schedules on delaying progression of disease and on overall survival in comparison with standard current treatments and chemotherapeutic regimens is not clear. Randomized clinical trials are required to evaluate precisely the role of rIL-2 in various therapeutic combinations and to ascertain the optimum therapeutic regimens for individual tumour types. Studies currently under way should provide more insight into the possible beneficial effects of immunotherapy with rIL-2. More basic research is required to ascertain how rIL-2 may produce its antitumour effects and why the therapeutic results obtained in humans have been so selective and less beneficial than those in experimental animals.

During the past two decades survival rates for leukaemia, lymphoma, testicular tumour and certain tumours of childhood have improved significantly as a result of advances in chemotherapy and radiotherapy. However, survival rates of patients with solid tumours (the largest group presenting to the surgeon) have not shown comparable improvement[1]. Minimal benefits in survival have been documented for breast, cervical, and head and neck cancers; no significant changes have been seen for patients with many other tumours, such as cancer of the stomach, pancreas or colorectum[1,2].

Therefore, despite continuing advances in surgical management, and in spite of the performance of more radical operations, substantial numbers of patients are still dying from disseminated disease, including many who have undergone apparently 'curative' surgery. Analysis of survival data from such patients and a better understanding of tumour biology suggest that, even when the lesion appears localized, occult metastatic disease is frequently present[3]. Modern surgery emphasizes both the need for effective control of local disease (with less radical and traumatic procedures, if possible) and the use of adjuvant therapy, wherever possible, to deal with metastatic disease and thus improve survival. Surgeons have also been in the forefront with the application of novel therapeutic approaches to disseminated disease (occult or metastatic), especially in the manipulation of anticancer host defences.

New strategies in the immunotherapy of cancer have centred on the use of biological response modifiers, especially the cytokines. These are soluble proteins secreted by lymphocytes and macrophages (as well as other cells) that act as intercellular regulatory molecules in an autocrine or paracrine manner. They are able to stimulate antitumour cytotoxic mechanisms or are themselves cytotoxic or cytostatic[4]. In particular, recent interest has centred on the cytokine interleukin (IL) 2, which is secreted by T helper lymphocytes and has been shown in various rodent tumour models to be effective in destroying established metastatic disease. The development of recombinant DNA technology has enabled the production of large quantities of recombinant interleukin 2 (rIL-2) for use in the treatment of malignant disease.

Since the mid-1980s, rIL-2 alone or in combination with other cytokines (e.g. interferons), activated lymphocytes (e.g. tumour-infiltrating lymphocytes) or lymphokine-activated killer (LAK) cells and various chemotherapeutic drugs, has been used with increasing frequency in the treatment of an expanding range of advanced malignancies. Conflicting data have been published in this rapidly growing area of therapy, especially from non-randomized studies that often comprise small patient groups. The time is opportune to review the published clinical data with a view to providing an up-to-date account of such therapy, particularly in relation to the treatment of advanced melanoma, renal cell carcinoma and colorectal cancer.

Interleukin 2 and host antitumour defences

Interleukin 2

IL-2 is a 15·5-kDa glycoprotein secreted by T helper lymphocytes following activation by antigens or mitogens that was originally described as a T cell growth factor[5,6]. Recombinant IL-2, produced by *Escherichia coli*, has identical effects to the native molecule although it is non-glycosylated. IL-2 has pleiotropic effects on the immune system but, in particular, it enhances natural cytotoxicity mediated by natural killer (NK) and LAK cells and increases substantially the lytic activity of the latter[7,8]. Animal studies have demonstrated that NK cells play a crucial role in the prevention of dissemination and establishment of tumour metastases[9]. LAK cells, with their cytotoxic effects against a wide range of cell types, are believed to be important in the destruction of malignant cells, particularly with cytokine-induced immunotherapy[10]. IL-2 induces the generation and activation of cytotoxic T cell subsets, whether restricted by the major histocompatibility complex or not[11,12], as well as stimulating the proliferation and activity of B lymphocytes[13]. IL-2 also activates macrophages, enhancing their cytotoxicity and, through its effect on various lymphoreticular cells, it is a key regulator of the secretion of various lymphokines – interferon (IFN) γ, IL-2, IL-4, and tumour necrosis factor (TNF) α and γ[7,14]. It is thus a key molecule, involved in modulating the normal immune response and in

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Table 1 *Possible mechanisms of antitumour effects of interleukin 2*

1. Stimulation of activity and proliferation of T and B lymphocytes and macrophages
2. Stimulation of activity and proliferation of natural killer and lymphokine-activated killer cells
3. Release of cytokines, e.g. interleukin 6, tumour necrosis factor α and interferon γ, that may also have an antitumour effect
4. Enhanced activation of endothelial cells and expression of adhesion molecules, which enables the migration of cells with antitumour activity into tissues

stimulating various host antitumour defence mechanisms, when given in pharmacological doses to patients with malignant disease.

IL-2 induces activation, differentiation and proliferation of lymphocytes and macrophages by interacting with specific receptors at the cell membrane. The receptor is composed of two polypeptide chains, α and β, each with three structural elements: an extracellular portion that binds IL-2, a transmembrane part and an intracellular component important in signal transduction (β chain)[15]. The α chain, also known as the p55 component, is recognized by the anti-Tac cluster differentiation 25 monoclonal antibody and has a molecular weight of 55 kDa. The β chain, the p70/75 component, has a molecular weight of 70–75 kDa and has a prominent intracellular portion. Monoclonal antibodies have recently become available that interact with the β chain and allow its demonstration using immunohistochemical techniques[16].

Effect on natural cytotoxicity and cytokines

Host antitumour defence mechanisms, in particular natural cytotoxicity mediated by NK and LAK cells, are thought to have an important role against malignant cells. NK cells have been shown in animal models to be important in removing circulating tumour cells and inhibiting the establishment of tumour metastases[9]. LAK cells, with their expanded repertoire of target-cell lysis and enhanced cytotoxic capabilities, have also been documented as playing a crucial role in causing regression of tumour deposits in animals[17–20]. However, the effect of rIL-2 on natural cytotoxicity in humans *in vivo* remains unclear. Some studies have shown that augmentation of NK cell activity is of prognostic significance in patients undergoing rIL-2 therapy[21,22], thus suggesting a possible antitumour role for NK cells in humans. In contrast, the LAK cell responses have been variable, with some studies documenting that increases in LAK cell cytotoxicity correlate with responses to therapy[22], while others have found that LAK cell cytotoxicity bears no relationship to the antitumour effect of rIL-2 administration[23,24]. These studies have often evaluated heterogeneous groups of patients, with different tumour types and treatment schedules. Studies by the present authors have evaluated the effect of a 5-day continuous infusion of rIL-2 on NK and LAK cell cytotoxicity in a group of 12 patients with advanced colorectal cancer[25]. These results showed that the activity of NK cells is maximally stimulated while the LAK cells undergo suboptimal stimulation *in vivo*; further coculture of these LAK cells with rIL-2 *in vitro* results in a substantial augmentation of their cytotoxic activity. The reasons for this inability to achieve maximal cytotoxicity *in vivo* are not clear, but preliminary data have indicated that serum levels of prostaglandins E_2 and $F_{2\alpha}$, which are implicated in the regulation of immunological function[26,27], are markedly increased in patients receiving rIL-2.

The changes in natural cytotoxicity described above were evaluated using peripheral blood lymphocytes. Other studies have evaluated the cellular infiltrates in tumour biopsies taken from patients undergoing rIL-2 therapy and have demonstrated the infiltration by various subsets of T lymphocytes and macrophages[28–30]. Interestingly, NK cells were virtually absent in the tumour biopsies after rIL-2 treatment, as they are in most tumour biopsies, but the reasons for this are unclear. The antitumour effect of rIL-2 therapy has been ascribed by some authors to the resultant cascade release of various other cytokines (*Table 1*).

IL-2 is known to stimulate the release of various other cytokines that may have an important role in host antitumour defences. In humans these mechanisms have been poorly documented, although the following effects have been described: (1) rIL-2 is known to stimulate the production of TNF-α from macrophages[31], which induces the release of free radicals and endonucleases[32] (antitumour effects); (2) rIL-2 stimulates the release of IFN-γ, which has antitumour actions (modulation of tumour oncogene expression and suppressor gene activity[33]); and (3) alteration of the tumour vasculature by TNF-α (causing necrosis and thrombosis), IFN-γ (inhibition of tumour angiogenesis)[34] and IL-1, TNF-α and IL-4 (enhancing expression of adhesion molecules and entrapment of inflammatory cells)[35].

Interleukin 2 and animal tumour models

Numerous animal experiments have demonstrated the efficacy of IL-2, given either alone or in combination with LAK cells intraperitoneally, in causing regression of pulmonary and hepatic metastases in a variety of experimental murine tumours, both immunogenic and non-immunogenic[17–20]. These studies, carried out by Rosenberg and colleagues, showed that there is a direct correlation between the dose of IL-2 infused and the number of LAK cells given, and the antitumour responses elicited. Also, IL-2 was able to increase LAK cell activity *in vivo*, the best responses being seen when both IL-2 and LAK cells were given concurrently. Infused LAK cells survived for prolonged periods *in vivo* and were also shown to target tumour cell deposits[36].

Further studies have demonstrated that the efficacy of IL-2 in mediating destruction of animal tumours can be increased when it is used in combination with IFN-α or TNF, or with tumour-infiltrating lymphocytes[37,38]. Following these encouraging results in animal tumour models, and the development of recombinant DNA technology with the resultant availability of large amounts of rIL-2, clinical studies were initiated in patients with malignant disease. In the latter part of the 1980s a number of publications appeared documenting the initial clinical experiences of the use of rIL-2 in human malignant disease that was refractory to conventional cancer therapy[23,39,40].

Interleukin 2 and malignant disease in humans

Therapeutic regimens in human studies

The most effective dose and mode of administration of rIL-2 have not yet been clearly defined. Animal experimental studies had suggested that continuous high serum levels of rIL-2 are necessary to obtain the maximal antitumour effect[41]. However, the initial human studies reported by Rosenberg *et al.*[39] used rIL-2 as an intravenous bolus given intermittently at high doses, up to 600 000 units per kg body-weight, at intervals of 8 h. Unfortunately this was associated with a high incidence of toxicity (often major complications), requiring most patients to be managed in an intensive care unit. In contrast, West and colleagues[23] administered lower doses of rIL-2 by a continuous intravenous infusion over a 5-day period. This appeared to produce a comparable clinical response rate with fewer complications. This also allowed the dose of rIL-2 to be altered (or stopped) as the patient's condition required and so enabled patients to be treated in standard oncology units.

Attempts have been made subsequently to evaluate the most effective dose of rIL-2 needed to stimulate host antitumour defence mechanisms in humans. Thompson *et al.*[42] administered the cytokine to groups of six patients at doses ranging from $3{\cdot}4 \times 10^5$ to $3{\cdot}4 \times 10^6$ units per m^2 body surface area per

24 h, given as a 2-h infusion, a 24-h infusion or injections at 8-h intervals. The *in vivo* activity of rIL-2, as assessed by expression of IL-2 receptors on lymphocytes, and LAK and NK cell activity, was more pronounced at the higher doses of rIL-2; the rebound lymphocytosis and IL-2 receptor expression were greater with the continuous infusion. West *et al.*[23] have attempted to define the most effective treatment schedule and relationship to enhancement of host defences. Their studies suggested that there is a threshold dose, 18×10^6 units per m^2 body surface area per day for 5 days, that is required to effect an *in vivo* lymphoproliferative response to rIL-2. There were no clinical responses seen when the cytokine was used in low doses. At higher doses, however, there were biological effects on immune mechanisms, although these did not necessarily result in effective antitumour responses.

Various combinations of cytokines have been used, for example rIL-2 combined with either TNF-α or IFN-α. Addition of TNF-α or IFN-α produced promising response rates but was associated with substantial toxicity[10]. Phase I studies with TNF-α and IL-1 alone have been disappointing and associated with substantial toxicity[10,43].

More recently, Atzpodien *et al.*[44] administered rIL-2 by twice-daily subcutaneous bolus injections, self-administered in an outpatient setting. The cytokine was administered in an escalating dose over 4 weeks, from $0{\cdot}3 \times 10^6$ to $2{\cdot}4 \times 10^6$ units per m^2 body surface area per day and then maintained at $1{\cdot}8 \times 10^6$ units per m^2 body surface area per week for up to 12 weeks. The regimen was effective in stimulating an increase in both the number and activity of NK and LAK cells, but was associated with a reduced incidence of toxicity compared with intravenous schedules. However, further well controlled studies are required to define more precisely the most effective treatment regimens (dose and method of administration) to achieve the maximal enhancement of antitumour defences and the most beneficial clinical effect, i.e. maximal reduction of tumour volume with minimal morbidity.

Recombinant interleukin 2 and renal cell cancer

Metastatic renal cell cancer is one of the most commonly documented tumours to show clinical evidence of spontaneous regression. Although earlier reports had suggested that this might occur in up to 7 per cent of patients[45], more recent analyses have documented that it occurs in fewer than 1 per cent of cases[46]. It is also one of the most frequently studied tumours, showing some of the best responses recorded with rIL-2 treatment.

Metastatic renal cell cancer has been treated with rIL-2 in non-randomized studies, either alone, in combination with LAK cells, with chemotherapy or with IFN-α. These studies[10,23,39,40,42,47–64] have involved variable numbers of patients; those reporting 20 or more patients are summarized in *Table 2*. Response rates, in terms of reduction of tumour volume, have ranged from zero to 37 per cent in studies reporting on at least ten patients. The duration of responses has ranged from 2 to 25 months. If all the responses from the different published studies are analysed together, the overall median duration of response is only 12 months. It can also be appreciated that rIL-2 alone has comparable response rates to rIL-2 combined with LAK cells and rIL-2 combined with IFN-α. However, the study using rIL-2 combined with cyclophosphamide failed to document a response in any of the patients treated.

The effect on survival of the cohorts of patients treated with different rIL-2 regimens is also poorly documented. Only three of the studies quoted have addressed this point; one reported a probability of survival of approximately 35 per cent at 12 months, and the three studies reported median survivals of 11·5, 12 and 18 months respectively[44,55,60]. Furthermore, only one of these studies attempted to compare the survival rate with historical controls. Philip *et al.*[55] reported a median survival of 8 months in historical controls. However, when patients were subsequently treated with rIL-2 (rIL-2 alone, rIL-2 plus LAK cells, rIL-2 combined with LAK cells and IFN-α), the median survival increased to 18 months. Recently, however, an analysis of patients treated with continuous infusions of rIL-2, compared with historical controls not receiving this cytokine, showed significant prolongations of overall survival in low-risk groups of patients but failed to demonstrate any benefit in high-risk groups[65].

Recombinant interleukin 2 and malignant melanoma

Spontaneous clinical and/or histological regression in malignant melanoma is well documented and not infrequent, although clinically beneficial spontaneous regression is rare. The current

Table 2 *Interleukin 2 and renal cell cancer*

Reference	Recombinant interleukin 2 regimen	No. of patients	Response rate (complete plus partial)* (%)	Duration of response (months)	Patient survival
Rosenberg *et al.*[10]	Intravenous bolus plus LAK cells	72	35	Median 9	Not stated
Rosenberg *et al.*[10]	Intravenous bolus	54	22	Median 25	Not stated
Blay *et al.*[31]	Intravenous infusion plus LAK cells	25	20	Not stated	Not stated
Rosenberg *et al.*[40]	Intravenous bolus	21	5	Complete: median 10	Not stated
Rosenberg *et al.*[40]	Intravenous bolus plus LAK cells	36	33	Partial: median 6	Not stated
von der Maase *et al.*[47]	Intravenous infusion	51	16	Median 12·3	35% at 12 months
Robertson *et al.*[49]	Intravenous bolus plus LAK cells plus TILs	94	31	Not stated	Not stated
Dillman *et al.*[52]	Intravenous infusion plus LAK cells	23	4	2	Not stated
Koretz *et al.*[53]	Intravenous infusion plus LAK cells	25	16	10·5	Not stated
Philip *et al.*[55]	Intravenous infusion plus LAK cells	22	18	Not stated	Median 18 months
Philip *et al.*[55]	Intravenous infusion plus LAK cells plus IFN-α	26	33	Not stated	
Atzpodien *et al.*[57]	Subcutaneous bolus plus subcutaneous IFN-α	27	37	Median 9·5	Not stated
Negrier *et al.*[61]	Intravenous infusion	22	14	Complete: 18 and 15 Partial: 4	Not stated
Thomas *et al.*[63]	Intravenous infusion plus IFN-α	22	5	1	Not stated

LAK, lymphokine-activated killer; TILs, tumour-infiltrating lymphocytes; IFN, interferon. *Complete response, no evaluable disease left; partial response, 50 per cent reduction in the product of the two maximum perpendicular diameters

Table 3 *Interleukin 2 and malignant melanoma*

Reference	Recombinant interleukin 2 regimen	No. of patients	Response rate (complete plus partial)* (%)	Duration of response (months)	Patient survival
Rosenberg *et al.*[10]	Intravenous bolus	54	22	2–41	Not stated
Rosenberg *et al.*[10]	Intravenous bolus plus LAK cells	48	21	2–52	Not stated
Rosenberg *et al.*[40]	Intravenous bolus plus LAK cells	26	23	Not stated	Not stated
Rosenberg *et al.*[43]	Intravenous bolus plus LAK cells	48	21	Median 9·5	Not stated
Rosenberg *et al.*[43]	Intravenous bolus	42	24	Median 8	Not stated
Dillman *et al.*[52]	Intravenous infusion plus LAK cells	33	12	Median 15	33% at 1 year
Gaynor *et al.*[54]	Intravenous infusion plus LAK cells	30	3	Median 8	Not stated
Dillman *et al.*[67]	Intravenous infusion plus LAK cells plus dacarbazine	27	26	Median 4	Median 10 months
Thatcher *et al.*[69]	Intravenous infusion (intrasplenic)	31	3	Not stated	Not stated
Demchak *et al.*[70]	Intravenous bolus plus cisplatin	27	37	Median 4	Not stated
Flaherty[71]	Intravenous bolus plus dacarbazine	29	24	Median 5	Not stated
Mitchell *et al.*[72]	Intravenous bolus plus cyclophosphamide	24	25	Median 6·5	Not stated

LAK, lymphokine-activated killer. *Complete response, no evaluable disease left; partial response, 50 per cent reduction in the product of the two maximum perpendicular diameters

Table 4 *Interleukin 2 and colorectal cancer*

Reference	Recombinant interleukin 2 regimen	No. of patients	Response rate (complete plus partial)* (%)	Duration of response (months)	Patient survival
Rosenberg *et al.*[10]	Intravenous bolus	12	0	No effect	Not stated
Rosenberg *et al.*[10]	Intravenous bolus plus LAK cells	30	17	Median 6	Not stated
West *et al.*[23]	Intravenous infusion plus LAK cells	13	0	No effect	Not stated
Rosenberg *et al.*[40]	Intravenous bolus plus LAK cells	26	12	Not known	Not stated
Mittelman *et al.*[51]	Intravenous infusion plus interferon α	10	0	No effect	Not stated
Hamblin *et al.*[75]	Intravenous infusion plus 5-fluorouracil	14	29	Not known	Not stated

LAK, lymphokine-activated killer. *Complete response, no evaluable disease left; partial response, 50 per cent reduction in the product of the two maximum perpendicular diameters

standard therapy for metastatic melanoma is chemotherapy, using a single agent (usually dacarbazine) or combination chemotherapy with dacarbazine and the nitrosoureas. Results from these studies have been reported by Legha[66]. Analysis of ten trials showed response rates ranging from 15 to 36 per cent for dacarbazine-based combination chemotherapy regimens, with the mean duration of response ranging from 3·5 to 9 (median 6·5) months.

Metastatic melanoma has been treated with rIL-2 alone, in combination with LAK cells, with chemotherapy, or with IFN-α[10,23,39,40,43,44,51–54,58,59,62–64,67–72]; the studies listed in *Table 3* are those reporting on more than 20 patients. Response rates have ranged from zero to 50 per cent when all these studies are considered. Various routes of administration and dosage schedules have been used without any obvious advantage for a particular regimen. However, there does appear to be a trend suggesting that better response rates are achieved when rIL-2 is used in combination with chemotherapy. Recent data have shown that cisplatin in combination with rIL-2 and IFN-α can achieve a response rate of up to 60 per cent, with approximately 20 per cent of patients achieving complete responses[73].

The duration of response, as assessed by tumour volume, has been documented in most of these studies. If all reported patients are considered together, this ranges from 1 to 52 months, with a median duration of response of only 6 months. Unfortunately, most of these studies do not report survival figures for patients. Only two studies have documented this information, with the first[67] reporting a 36 per cent probability of survival at 1 year and the second[52] a 33 per cent probability.

Recombinant interleukin 2 and colorectal cancer

Patients with metastatic colorectal cancer have been treated with rIL-2 alone, in combination with chemotherapy (5-fluorouracil; 5-FU) or LAK cells and, more recently, with IFN-α[10,23,39,40,42,44,51,52,59,60,74–77]. These studies, with small numbers of patients in each series, have used different doses, modes of administration of rIL-2 (continuous intravenous infusion, bolus injection or the subcutaneous route) and different treatment schedules. *Table 4* summarizes studies reporting on at least ten patients. Response rates ranging from zero to 33 per cent have been reported. However, the duration of the response was not stated in these studies, except for one in which there was a median duration of response of 6 months. Furthermore, the overall survival for the cohorts of patients treated with rIL-2 was not documented in any of these studies. To date there have been no published data from randomized trials comparing rIL-2 therapy with current chemotherapeutic regimens, although such a study is in progress. It is, therefore, difficult to draw generalizations or conclusions regarding the role of rIL-2 in colorectal cancer. However, it appears that: (1) if rIL-2 is used alone there is little likelihood of a clinical response; (2) the dose and mode of administration of rIL-2 do not affect the response to therapy; (3) the best responses

Table 5 *Morbidity of recombinant interleukin 2 therapy*

System	Effect
General	Pyrexia, myalgia, anorexia, fatigue, 'flu-like illness, weight gain
Cardiovascular	Hypotension, angina, myocardial infarction, arrhythmia, peripheral oedema
Respiratory	Bronchospasm, pleural effusions, respiratory distress syndrome, pulmonary oedema
Renal	Oliguria, increased serum urea and creatinine levels, acute renal failure, decreased glomerular filtration rate, abnormalities in tubular handling of sodium and water, enzymuria
Dermatological	Pruritus, skin rashes, photosensitivity, desquamation
Haematological	Anaemia, thrombocytopenia
Central nervous system	Confusion, disorientation, coma, convulsions
Peripheral nervous system	Carpal tunnel syndrome
Gastrointestinal	Nausea, vomiting, diarrhoea, liver dysfunction
Endocrine	Thyroid dysfunction

have occurred when rIL-2 was used with LAK cells, but this was associated with increased treatment-related toxicity; and (4) promising results have been reported for rIL-2 used in conjunction with 5-FU.

The combination of 5-FU and leucovorin (folinic acid) has been demonstrated to be more effective than 5-FU alone in prolonging overall survival and time to progression of disease in patients with advanced colorectal malignancy. Furthermore, response rates of up to 42 per cent, and 12- and 24-month survival rates of 40 and 20 per cent, respectively, have been reported in some series[78,79]. In view of this, a European phase III trial with UK participants is currently being conducted comparing rIL-2–5-FU–leucovorin with 5-FU–leucovorin alone to help further clarify the role of rIL-2. In this trial the chemotherapy schedule (weekly pulses of 5-FU–leucovorin) is different from that of studies reporting some of the best results with chemotherapy. The response rate to rIL-2–5-FU–leucovorin to date in the authors' small series of trial-participating patients is encouraging, but detailed analysis of the results from all participating centres needs to be carried out before any definitive conclusions can be drawn about the use of rIL-2 and chemotherapy for locally advanced or metastatic colorectal cancer.

Morbidity associated with recombinant interleukin 2 treatment

Initial studies in humans reported considerable morbidity and also mortality associated with high doses of rIL-2 administered by bolus infusions[39,40]. Some of the side-effects are shown in *Table 5*. These side-effects, however, are less common and less severe with the administration of moderate doses of rIL-2 given by continuous infusion, e.g. 18 × 10^6 units per m^2 body surface area per 24 h, and resolve within 24–48 h after stopping treatment[23]. The subcutaneous route of administration is associated with even fewer and milder side-effects: inflammation at the skin injection site, fever, 'flu-like illness, nausea and vomiting[59]. This route allows patients to be treated in an outpatient setting or even to administer the treatment to themselves at home. A treatment-related mortality rate of 1·5 per cent has been documented in the largest reported series of 652 patients receiving rIL-2 by bolus doses[10], which is not dissimilar to the mortality rate associated with some of the currently used combination chemotherapy schedules.

General effects. Most patients experience a 'flu-like illness characterized by a prominent pyrexia, anorexia, malaise, myalgia and arthralgia.

Cardiopulmonary effects. A major cause for this toxicity appears to be the 'vascular leak' syndrome[80]. It has been suggested that vascular endothelial cells express activation antigens or adhesion molecules that are increased in number by high levels of circulating cytokines. Circulating NK and LAK cells interact with the endothelium, resulting in capillary cell changes and enhanced vascular leakage of macromolecules, water and sodium[81], resulting in a reduction in systolic blood pressure. Recent evidence suggests that rIL-2 enhances nitric oxide production from L-arginine which then induces vasodilatation[82]. This hypotension is usually treated with infusion of crystalloid or colloid solutions, but in some studies, especially with high doses of bolus rIL-2 infusions, pressor agents (dopamine or phenylephrine) have been necessary. If the blood pressure cannot be controlled and falls to <75–80 mmHg, rIL-2 should be temporarily withheld; this usually leads to a rapid return to normal levels. Furthermore, arrhythmia, angina, myocardial infarction and reductions of left ventricular ejection fraction have also occurred[10,39,40,83].

Renal dysfunction. Renal dysfunction has been characterized by oliguria, decreased glomerular filtration rate and raised serum urea and creatinine levels, and in some series has been found to be treatment-limiting[10,37,76,84]. Studies by the present authors involving lithium clearance measurements and urinary enzyme levels have demonstrated marked alterations in the proximal and distal nephron handling of sodium and water that can persist for prolonged periods of time despite normal serum urea and creatinine levels[85]. It is believed that the relative hypotension induced by the vascular leak syndrome, in conjunction with a rIL-2-induced inhibition of secretion of vasodilator prostaglandins, is an important factor in the pathogenesis of renal dysfunction. In some studies this change in prostaglandin levels has been further compounded by the use of prostaglandin synthetase inhibitors to treat the rIL-2-induced pyrexia. Clinically relevant renal toxicity has been reduced by avoiding the use of these drugs to treat the pyrexia and 'flu-like symptoms[86].

Dermatological effects. The majority of patients experience a generalized erythema, maculopapular rash, pruritus and variable degrees of desquamation. Exacerbations of pre-existing skin problems, such as psoriasis and seborrhoeic dermatitis, may also occur[87]. The histological features of this skin rash are non-specific, although increased expression of adhesion molecules has been shown, e.g. intercellular adhesion molecule 1 on keratinocytes, endothelial cells and the perivascular cellular infiltrate in biopsies taken from these patients[88].

Haematological effects. Treatment with rIL-2 may produce anaemia, eosinophilia, lymphopenia and thrombocytopenia. The lymphopenia occurring during treatment is of particular interest, but why it occurs is unknown. Within 24–48 h of stopping rIL-2 therapy there is a marked rebound lymphocytosis that is related to the mode and dose of rIL-2 administration[10,23,39]. After cessation of therapy the haematological side-effects disappear.

Neuropsychiatric effects. Neuropsychiatric effects have often been documented[10,23,39,89]. Restlessness, confusion, convulsions and changes in cognitive function and behaviour may occur. Peripheral nerve entrapment may also occur and the present authors have seen two patients who developed carpal tunnel syndrome, one of whom required operative decompression which was followed by a complete neurological recovery[90].

Gastrointestinal effects. Anorexia, nausea, vomiting and diarrhoea are common side-effects, occurring to a variable degree in most patients[10,69]; they are controlled by symptomatic measures. Gastric and duodenal ulceration have also been reported, although the patients were also receiving non-steroidal anti-inflammatory drugs[91]. Abnormalities of liver function have been noted with increased serum bilirubin, aspartate aminotransferase and alkaline phosphatase levels[92].

Endocrine effects. The hormonal effects of rIL-2 treatment are of two types, with changes occurring either secondary to an acute inflammatory process or to chronic inflammatory changes associated with an autoimmune type of disease process[91]. A variety of hormones may be stimulated by rIL-2, such as adrenocorticotrophic hormone, β endorphin and cortisol[40,89,93]. Thyroid function, in particular, has been investigated as approximately 20 per cent of patients may become hypothyroid, although most of these have pre-existing thyroid autoantibodies. It is also interesting that one study found a higher response rate to rIL-2 in those who became hypothyroid[94].

Prediction of patients responding to recombinant interleukin 2 therapy

If at best only 40 per cent of patients have a complete or partial response to rIL-2 therapy, it would be beneficial in terms of costs (social, financial, etc.) and the avoidance of treatment-related morbidity to be able to predict which patients were most likely to respond. Attempts have been made to do this. West *et al.*[23] have suggested that a favourable response to treatment can be predicted by measuring the pretreatment absolute lymphocyte count or the degree of rebound lymphocytosis following cessation of rIL-2 treatment. Others, however, have not found these parameters to be of predictive value[24]. Enhancement of natural cytotoxicity, e.g. NK and LAK cell activity *in vitro* or *in vivo*, has been used as a predictor[21,22]. Sustained production of TNF-α after cessation of rIL-2 therapy and release of various cytokines such as TNF-α and IL-6 have also been used in some studies[31,95]. Clinical factors such as performance index, site and extent of disease (lung and lymph node metastases respond better than liver metastases) have been used to try to estabish a predictive index. Unfortunately, none of these indices has proven reliable. Furthermore it appears that the response is dependent on tumour type, as the best results have consistently been obtained in patients with renal cell tumours and malignant melanoma.

Recently, however, interest has centred on the interrelationship of the cytokine system and the acute-phase proteins as it is known that hepatic synthesis of the latter is regulated by cytokines, in particular IL-1, IL-6 and TNF-α[96]. The present authors have measured the serum concentration of several acute-phase proteins, including C-reactive protein (CRP), both before and during infusion of rIL-2 in 15 patients with metastatic colorectal cancer[97]. These studies have demonstrated that in patients who responded to rIL-2 therapy the baseline pretreatment CRP level was <10 mg/l. Also, the responding patients demonstrated a significant increase in CRP concentration during rIL-2 infusion. In contrast, non-responding patients had a significantly raised pretreatment CRP level and, furthermore, all patients failed to demonstrate a significant rise in CRP during subsequent rIL-2 treatment. Serum CRP level can be measured in most hospital laboratories; the assay is inexpensive and the results obtained relatively quickly. Further studies need to be carried out with larger groups of subjects and different tumour types to define more precisely the relevance of the acute-phase response to immunotherapy.

Future developments in the use of recombinant interleukin 2 in malignant disease

Animal studies have shown beneficial and synergistic results when rIL-2 is used in combination with other methods of immunotherapy. In particular, combinations of IFN-α, TNF-α and monoclonal antibodies with rIL-2 gave improved results compared with rIL-2 alone[39,98,99]. Further work is required in patients with malignancy to evaluate these combinations in terms of enhanced clinical response and reduced morbidity. Preliminary studies from Rosenberg *et al.*[10] have suggested that rIL-2 used in combination with IFN-α is also more effective than rIL-2 alone, without additional treatment-related toxicity, but other workers have not confirmed this. Recent interest has also focused on tumour-infiltrating lymphocytes. Isolation of these lymphocytes and subsequent reinfusion back into a tumour-bearing animal has resulted in very efficient destruction of metastatic tumour deposits, more so than with LAK cells[100]. Human tumour-infiltrating lymphocytes have been isolated and expanded in *in vitro* culture with rIL-2. Such cells have subsequently been used in treatment and the initial results look promising[10]. These techniques are labour-intensive and costly and other methods of generating more effective tumour-infiltrating lymphocytes such as gene transfection are being pursued.

The use of biological response modifiers in combination with chemotherapy has been shown to achieve better response rates than immunotherapy alone in certain types of tumour. Although many chemotherapeutic agents, e.g. cyclophosphamide, cause immunosuppression at conventional doses, they are immunostimulative at lower doses[101]. Therefore, specific combinations of chemotherapeutic agents and biological response modifiers, given in defined sequences, may offer improved response rates in certain malignancies.

The use of rIL-2 has so far been restricted to the treatment of advanced malignancy. However, preliminary work has indicated that rIL-2 may be used in the perioperative period to reverse the immunosuppression associated with surgical trauma[102]. This is a period when tumour cell dissemination is occurring and the use of rIL-2 as an adjuvant therapy in the treatment of surgically 'curable' tumours offers exciting possibilities.

References

1. *Cancer patient survival: what progress has been made?* Report to Chairman, Subcommittee on Intergovernmental Relations and Human Resources, Committee on Government Operations, House of Representatives, Gaithersburg, Maryland. US General Accounting Office Publication POB 6015, 1987.
2. Williams NS. Changing pattern in the treatment of rectal cancer. *Br J Surg* 1988; **76**: 5–6.
3. Brinkley D, Haybittle JL. Long term survival of women with breast cancer. *Lancet* 1984; **i**: 1118–19.
4. Guillou PJ. Immunological approaches to the treatment of malignant disease. *J R Coll Surg Edinb* 1988; **33**: 2–8.
5. Morgan DA, Ruscetti FW, Gallo R. Selective *in vitro* growth of T lymphocytes from normal human bone marrows. *Science* 1976; **193**: 1007–10.
6. Gillis S, Ferm MM, Ou W, Smith KA. T cell growth factor: parameters of production and a quantitative microassay for activity. *J Immunol* 1978; **120**: 2027–33.
7. Ortaldo JR, Mason TA, Gerard JP *et al.* Effects of natural and recombinant IL2 on regulation of gamma IFN production and natural killer cell activity: lack of involvement of the TAC antigen for these immunoregulatory effects. *J Immunol* 1984; **133**: 779–83.
8. Grimm EA, Robb RJ, Roth JA *et al.* Lymphokine-activated killer cell phenomenon III. Evidence that IL2 is sufficient for direct activation of peripheral blood lymphocytes into lymphokine-activated killer cells. *J Exp Med* 1983; **158**: 1356–61.
9. Gorelik E, Wiltrout RH, Okumura K, Habu S, Herberman RB. Role of NK cells in the control of metastatic spread and growth of tumour cells in mice. *Int J Cancer* 1982; **30**: 107–12.
10. Rosenberg SA, Lotze MT, Yang JC *et al.* Experience with the use of high-dose interleukin-2 in the treatment of 652 cancer patients. *Ann Surg* 1989; **210**: 474–85.
11. Watson J, Mochuzuki D. Interleukin 2: a class of T cell growth factors. *Immunol Rev* 1980; **51**: 257–78.
12. Rosenberg SA. What's new in general surgery? The development of new immunotherapies for the treatment of cancer using interleukin 2. *Ann Surg* 1988; **208**: 121–35.
13. Zubler RH, Lowenthal JW, Erard F *et al.* Activated B cells express receptors for, and proliferate in response to, pure interleukin-2. *J Exp Med* 1984; **160**: 1170–83.
14. Kurt-Jones EA, Hamberg S, Ohara J, Paul WE, Abbas AK.

Heterogeneity of helper/inducer T lymphocytes. *J Exp Med* 1987; **166**: 1774–89.

15. Kuziel WA, Greene WC. Interleukin-2. In: Thomson AW, ed. *The Cytokine Handbook*. London: Academic Press, 1991: 83–102.
16. Takeshita T, Goto Y, Tada K, Hagata K, Asao H, Sugumura K. Monoclonal antibody defining a molecule possibly identical to the p75 subunit of the interleukin 2 receptor. *J Exp Med* 1989; **169**: 1323–32.
17. Lafreniere RL, Rosenberg SA. Adoptive immune therapy of murine hepatic metastases and recombinant-IL2 can mediate the regression of both immunogenic and non-immunogenic sarcomas and an adenocarcinoma. *J Immunol* 1985; **135**: 4273–80.
18. Mule JJ, Shu S, Rosenberg SA. The anti-tumor efficacy of lymphokine-activated killer cells and recombinant interleukin 2 *in vivo*. *J Immunol* 1985; **135**: 646–52.
19. Lafreniere RL, Rosenberg SA. Successful immunotherapy of murine experimental metastases with lymphokine-activated killer cells and recombinant interleukin 2. *Cancer Res* 1985; **45**: 3735–41.
20. Mule JJ, Shu SL, Schwarz SL, Rosenberg SA. Adoptive immunotherapy of established pulmonary metastases with LAK cells and recombinant interleukin-2. *Science* 1984; **225**: 1487–9.
21. Hayat K, Rodgers S, Bruce L *et al.* Malignant melanoma and renal cell carcinoma: immunological and haematological effects of recombinant human interleukin-2. *Eur J Cancer* 1991; **27**: 1009–14.
22. Walewski J, Paietta E, Dutcher J, Wiernik PH. Evaluation of natural killer and lymphokine-activated killer (LAK) cell activity *in vivo* in patients treated with high-dose interleukin-2 and adoptive transfer of autologous LAK cells. *J Cancer Res Clin Oncol* 1989; **115**: 170–4.
23. West WH, Tauer KW, Yannelli JR *et al.* Constant-infusion recombinant interleukin-2 in adoptive immunotherapy of advanced cancer. *N Engl J Med* 1987; **316**: 898–905.
24. Boldt DH, Mills BJ, Gemlo BT *et al.* Laboratory correlates of adoptive immunotherapy with recombinant interleukin-2 and lymphokine-activated killer cells in humans. *Cancer Res* 1988; **48**: 4409–16.
25. Park KGM, Heys SD, Murray JB *et al.* Recombinant interleukin 2 (rIL2) treatment in patients with metastatic colorectal cancer: effect on natural cytotoxicity. *Cancer Immunol Immunother* 1992; **35**: 53–8.
26. Bankhurst AD. The modulation of human natural killer activity by prostaglandins. *J Clin Lab Immunol* 1982; **7**: 85–91.
27. Imir T, Sibbitt W, Bankhurst A. The relative resistance of lymphokine-activated killer cells to suppression by prostaglandins and glucocorticoids. *Prostaglandins, Leukotrienes, and Medicine* 1987; **28**: 111–18.
28. Cohen PJ, Lotze MT, Roberts JR, Rosenberg SA, Jaffe ES. The immunopathology of sequential tumor biopsies in patients treated with interleukin-2. *Am J Pathol* 1987; **129**: 208–16.
29. Rubin JT, Elwood LJ, Rosenberg SA, Lotze MT. Immunohistochemical correlates of response to recombinant interleukin-2-based immunotherapy in humans. *Cancer Res* 1989; **49**: 7086–92.
30. Winchester RJ, Kunkel HG. The human Ia system. *Adv Immunol* 1979; **28**: 221–92.
31. Blay J-Y, Favrot MC, Negrier S *et al.* Correlation between clinical response to interleukin 2 therapy and sustained production of tumor necrosis factor. *Cancer Res* 1990; **50**: 2371–4.
32. Spriggs DR. Tumor necrosis factor: basic principles and preclinical studies. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Biological Therapy of Cancer*. Philadelphia, Pennsylvania: JB Lippincott, 1991: 354–77.
33. Kurzrock R, Talpaz M, Gutterman JU. Interferons-α,β,γ: basic principles and preclinical studies. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Biological Therapy of Cancer*. Philadelphia, Pennsylvania: JB Lippincott, 1991: 247–74.
34. Tsuruoka T, Sugiyama M, Tawaragi Y *et al.* Inhibition of *in vitro* angiogenesis by lymphotoxin and interferon gamma. *Biochem Biophys Res Commun* 1888; **155**: 429–35.
35. Shimizu Y, Newman W, Tanaka Y, Shaw S. Lymphocyte interactions with endothelial cells. *Immunol Today* 1992; **13**: 106–12.
36. Mule JJ, Yang J, Shu S, Rosenberg SA. The anti-tumor efficacy of lymphokine-activated killer cells and recombinant interleukin 2 *in vivo*: direct correlation between reduction of established metastases and cytolytic activity of lymphokine-activated killer cells. *J Immunol* 1986; **136**: 3899–909.
37. McIntosh JK, Mule JJ, Krosnick JA, Rosenberg SA. Combination cytokine immunotherapy with tumor necrosis factor, interleukin-2 and alpha-interferon and its synergistic antitumor effects in mice. *Cancer Res* 1989; **49**: 1408–14.
38. Papa MZ, Mule JJ, Rosenberg SA. The antitumor efficacy of lymphokine-activated killer cells and recombinant interleukin-2 *in vivo*: successful immunotherapy of established pulmonary metastases from weakly- and non-immunogenic murine tumors of three distinct histologic types. *Cancer Res* 1986; **46**: 4973–8.
39. Rosenberg SA, Lotze MT, Muul LM *et al.* Observations on the systemic administration of autologous lymphokine-activated killer cells and recombinant interleukin-2 to patients with metastatic cancer. *N Engl J Med* 1985; **313**: 148–92.
40. Rosenberg SA, Lotze MT, Muul LM *et al.* A progress report on the treatment of 157 patients with advanced cancer using lymphokine-activated killer cells and interleukin-2 or high-dose interleukin-2 alone. *N Engl J Med* 1987; **316**: 889–97.
41. Ettinghausen SE, Rosenberg SA. Immunotherapy of murine sarcomas using lymphokine-activated killer cells: optimization of the schedule and route of administration of recombinant interleukin-2. *Cancer Res* 1986; **46**: 2784–92.
42. Thompson JA, Lee DL, Lindgren CG *et al.* Influence of dose and duration of infusion of interleukin-2 on toxicity and immunomodulation. *J Clin Oncol* 1988; **6**: 669–78.
43. Rosenberg SA, Lotze MT, Yang JC *et al.* Combination therapy with interleukin-2 and alpha-interferon for the treatment of patients with advanced cancer. *J Clin Oncol* 1989; **7**: 1863–74.
44. Atzpodien J, Korfer A, Evers P *et al.* Low-dose subcutaneous recombinant interleukin-2 in advanced human malignancy: a phase II outpatient study. *Mol Biother* 1990; **2**: 18–26.
45. DeKernion JB, Berry D. The diagnosis and treatment of renal cell carcinoma. *Cancer* 1980; **45**: 1947–56.
46. Oliver RTD, Nethersall AB, Bottomley JM. Unexplained spontaneous regression and alpha-interferon as treatment for metastatic renal cell carcinoma. *Br J Urol* 1989; **63**: 128–31.
47. von der Maase H, Geertsen P, Thatcher N *et al.* Recombinant interleukin-2 in metastatic renal cell carcinoma – a European multicentre phase II study. *Eur J Cancer* 1991; **27**: 1583–9.
48. Abrams JS, Rayner AA, Wiernik PH *et al.* High-dose recombinant interleukin-2 alone: a regimen with limited activity in the treatment of advanced renal cell carcinoma. *J Natl Cancer Inst* 1990; **82**: 1202–6.
49. Robertson CN, Linehan WM, Pass HI *et al.* Preparative cytoreductive surgery in patients with metastatic renal cell carcinoma treated with adoptive immunotherapy with interleukin-2 or interleukin-2 plus lymphokine-activated killer cells. *J Urol* 1990; **144**: 614–18.
50. Bukowski RM, Sharfman W, Murthy S *et al.* Clinical results and characterization of tumor-infiltrating lymphocytes with or without recombinant interleukin-2 in human metastatic renal cell carcinoma. *Cancer Res* 1991; **51**: 4199–205.
51. Mittelman A, Huberman M, Puccio C *et al.* A phase I study of recombinant human interleukin-2 and alpha-interferon-2a in patients with renal cell cancer, colorectal cancer, and malignant melanoma. *Cancer* 1990; **66**: 664–9.
52. Dillman RO, Oldham RK, Tauer KW *et al.* Continuous interleukin-2 and lymphokine-activated killer cells for advanced cancer: a National Biotherapy Study Group trial. *J Clin Oncol* 1991; **9**: 1233–40.
53. Koretz MJ, Lawson DH, York RM *et al.* Randomized study of interleukin 2 (IL-2) alone *vs* IL-2 plus lymphokine-activated killer cells for treatment of melanoma and renal cell cancer. *Arch Surg* 1991; **126**: 898–903.
54. Gaynor ER, Weiss GR, Margolin KA *et al.* Phase I study of high-dose continuous-infusion recombinant interleukin-2 and autologous lymphokine-activated killer cells in patients with metastatic or unresectable malignant melanoma and renal cell carcinoma. *J Natl Cancer Inst* 1990; **82**: 1397–402.
55. Philip T, Negrier S, Mercatello A *et al.* Interleukin-2 in the treatment of metastatic renal cell cancer: 77 patients treated in Lyon. *Insights into Immunotherapy* 1990; **1**: 23–30.
56. Galligioni E, Sorio R, Quaia M *et al.* Clinical aspects of treatment with recombinant interleukin-2 in metastatic renal cell cancer: experience of the comprehensive cancer centre, Aviano, Italy. *Insights into Immunotherapy* 1990; **1**: 37–40.
57. Atzpodien J, Kirchner H, Franks CR *et al.* Outpatient treatment of advanced human cancer using a combination of recombinant interleukin-2 and interferon-α2b. *Insights into Immunotherapy* 1990; **1**: 47–9.
58. Lindemann A, Hoeffken K, Schmidt RE *et al.* A multicentre

trial of interleukin-2 and low-dose cyclophosphamide in highly chemotherapy-resistant malignancies. *Cancer Treat Rev* 1989; **16**(Suppl 1): 53–7.

59. Atzpodien J, Korfer A, Franks CR, Poliwoda H, Kirchner H. Home therapy with recombinant interleukin-2 and interferon-α2b in advanced human malignancies. *Lancet* 1990; **335**: 1509–12.
60. Lissoni P, Barni S, Ardizzoia A *et al.* Second line therapy with low-dose subcutaneous interleukin-2 alone in advanced renal cancer patients resistant to interferon-alpha. *Eur J Cancer* 1992; **28**: 92–6.
61. Negrier S, Mercatello A, Bret M *et al.* Intravenous interleukin-2 in patients over 65 with metastatic renal carcinoma. *Br J Cancer* 1992; **65**: 723–6.
62. Vasveld LT, Rankin EM, Hekman A *et al.* A phase I study of prolonged continuous infusion of low dose recombinant interleukin-2 in melanoma and renal cell cancer. Part I: clinical aspects. *Br J Cancer* 1992; **65**: 744–50.
63. Thomas H, Barton C, Saini A, Dalgleish A, Waxman J. Sequential interleukin-2 and alpha interferon for renal call carcinoma and melanoma. *Eur J Cancer* 1992; **28A**: 1047–9.
64. Leahy MG, Pitfield D, Popert S, Gallagher CJ, Oliver RDT. Phase I study comparing continuous infusion of recombinant interleukin-2 by subcutaneous or intravenous administration. *Eur J Cancer* 1992; **28A**: 1049–51.
65. Jones M, Selby P, Bradley C *et al.* Advanced renal cancer treated by interleukin-2 continuous infusion: comparison of survival to a matched control group. *Proceedings of the Immunobiology of Renal Cell Cancer* 1993 (in press).
66. Legha SS. Current therapy for malignant melanoma. *Semin Oncol* 1989; **16**(Suppl 1): 34–44.
67. Dillman RO, Oldham RK, Barth NM *et al.* Recombinant interleukin-2 and adoptive immunotherapy alternating with dacarbazine therapy in melanoma: a National Biotherapy Study Group trial. *J Natl Cancer Inst* 1990; **82**: 1345–9.
68. Stoter G, Shiloni E, Gundersen S *et al.* Alternating recombinant interleukin-2 and dacarbazine in advanced melanoma. A multicentre phase II study. *Cancer Treat Rev* 1989; **16**(Suppl 1): 59–63.
69. Thatcher N, Dazzi H, Gosh A, Johnson RJ. Recombinant IL-2 given intrasplenically and intravenously in advanced malignant melanoma: a phase I/II study. *Cancer Treat Rev* 1989; **16**(Suppl 1): 49–52.
70. Demchak PA, Mier JW, Robert NJ, O'Brien K, Gould JA, Atkins MB. Interleukin-2 and high-dose cisplatin in patients with metastatic melanoma: a pilot study. *J Clin Oncol* 1991; **9**: 1821–30.
71. Flaherty L. The combination of recombinant interleukin-2 and dacarbazine (DTIC) in metastatic melanoma. *Cancer Treat Rev* 1989; **16**(Suppl 1): 65–6.
72. Mitchell MS, Kempf RA, Harel W *et al.* Effectiveness and tolerability of low-dose cyclophosphamide and low-dose intravenous interleukin-2 in disseminated melanoma. *J Clin Oncol* 1988; **6**: 409–24.
73. Kyahat D, Borel Ch, Antoine E *et al.* Highly active chemoimmunotherapy (cisplatin (P)-IL2-alpha-interferon (IFN)) in the treatment of metastatic malignant melanoma. *Proceedings of the American Society of Clinical Oncology* 1992; **11**: 1213A.
74. Hamblin TJ, Inzani V, Sadullah S *et al.* A phase-II trial of recombinant interleukin-2 and 5-FU chemotherapy in patients with metastatic carcinoma. *Cancer Treat Rev* 1989; **16**(Suppl 1): 163–7.
75. Hamblin TJ, Williamson PJ, George DK, Oskam R, Palmer PA, Franks CR. A phase II study of human r-IL2 and 5FU chemotherapy in the treatment of metastatic colorectal carcinoma. *Proceedings of the American Society of Clinical Oncology* 1990; **9**: 433A.
76. Lotze MT, Matory YL, Rayner AA *et al.* Clinical effects and toxicity of interleukin-2 in patients with cancer. *Cancer* 1986; **58**: 2764–72.
77. Eremin O, Heys SD, Park KGM *et al.* Interleukin 2 therapy in patients with hepatic metastases. *Eur J Surg Oncol* 1992; **18**: 406A.
78. Laufman LL, Brenckman WD Jr, Stydnicki KA *et al.* Clinical experience with leucovorin and 5-fluorouracil. *Cancer* 1989; **63**: 1031–5.
79. Bruckner HW, Motwani BT. Chemotherapy of advanced cancer of the colon and rectum. *Semin Oncol* 1991; **18**: 443–61.
80. Ettinghausen SE, Puri RK, Rosenberg SA. Increased vascular permeability in organs mediated by the systemic administration of lymphokine-activated killer cells and recombinant interleukin-2 in mice. *J Natl Cancer Inst* 1988; **80**: 177–88.
81. Damle NK, Doyle LV. IL-2 activated human killer lymphocytes but not their secreted products mediate increase in albumin flux across cultured endothelial monolayers. *J Immunol* 1989; **42**: 2660–9.
82. Hibbs JB, Westenfelder C, Taintor R *et al.* Evidence for cytokine-inducible nitric oxide synthesis from L-arginine in patients receiving interleukin-2 therapy. *J Clin Invest* 1992; **89**: 867–77.
83. Kozemy GA, Nicolas JD, Sticklin L *et al.* Effects of interleukin-2 immunotherapy on renal function. *J Clin Oncol* 1988; **6**: 1170–6.
84. Belldegrun A, Webb DE, Austin HA *et al.* Effects of interleukin-2 on renal function in patients receiving immunotherapy for advanced cancer. *Ann Intern Med* 1987; **106**: 817–22.
85. Heys SD, Eremin O, Broom J, Whiting PH. Lithium clearance measurements during interleukin 2 therapy: an index of tubular function in man. *Ren Fail* 1993 (in press).
86. Hamblin TJ. Interleukin 2. Side effects are acceptable. *BMJ* 1990; **300**: 275–6.
87. Gaspari AA, Lotze MT, Rosenberg SA, Stern JB, Katz SI. Dermatological changes associated with interleukin-2 administration. *JAMA* 1987; **258**: 1624–9.
88. Blessing K, Park KGM, Heys SD, King G, Eremin O. Immunopathological changes in the skin following recombinant interleukin-2 treatment. *J Pathol* 1992; **167**: 313–19.
89. Denikoff KD, Rubinow DR, Papa MZ *et al.* The neuropsychiatric effects of treatment with interleukin-2 and lymphokine-activated killer cells. *Ann Intern Med* 1987; **107**: 292–300.
90. Heys SD, Mills KLG, Eremin O. Bilateral carpal tunnel syndrome associated with interleukin-2 therapy. *Postgrad Med J* 1992; **68**: 587–8.
91. Parkinson DR. Interleukin-2 in cancer patients. *Semin Oncol* 1988; **15**(Suppl 6): 10–26.
92. Fisher B, Keenan AM, Garro BS *et al.* Interleukin-2 induces profound reversible cholestasis: a detailed analysis in treated cancer patients. *J Clin Oncol* 1989; **7**: 1–11.
93. Lotze MT, Frana LW, Sharrow SO *et al.* *In vivo* administration of purified human interleukin-2. I. Half-life and immunologic effects of the Jurkat cell line-derived interleukin-2. *J Immunol* 1985; **134**: 157–66.
94. Atkins MB, Mier JW, Parkinson DR *et al.* Hypothyroidism after treatment with interleukin-2 and lymphokine-activated killer cells. *N Engl J Med* 1988; **318**: 1557–63.
95. McIntyre CA, Chapman K, Reeder S *et al.* Treatment of malignant melanoma and renal cell carcinoma with recombinant interleukin-2: analysis of cytokine levels in sera and culture supernatants. *Eur J Cancer* 1992; **28**: 58–63.
96. Gauldie J, Richards C, Harnish D *et al.* Interferon β_1 is identical to monocyte HSF and regulates the full acute phase protein response in liver cells. In: Powanda JC, Oppenheim JJ, Kluger MJ, Dinarello CA, eds. *Monokines and Other Non-lymphocytic Lymphokines*. New York: Alan R Liss, 1988: 15–20.
97. Broom J, Heys SD, Whiting PH *et al.* Interleukin 2 therapy in cancer: identification of responders. *Br J Cancer* 1993 (in press).
98. Rosenberg SA. Immunotherapy of cancer using interleukin 2: current status and future prospects. *Immunol Today* 1988; **9**: 58–62.
99. McIntosh JK, Mule JJ, Krosnick JA, Rosenberg SA. Combination cytokine immunotherapy with tumor necrosis factor, interleukin-2 and alpha-interferon and its synergistic antitumor effects in mice. *Cancer Res* 1989; **49**: 1408–14.
100. Rosenberg SA, Spiess P, Lafreniere R. A new approach to the adoptive immunotherapy of cancer with tumor-infiltrating lymphocytes. *Science* 1986; **233**: 1318–21.
101. Mitchell M. Principles of combining biomodulators with cytotoxic agents *in vivo*. *Semin Oncol* 1992; **19**(Suppl 4): 51–6.
102. Nichols PH, Ramsden CW, Ward U, Sedman PC, Primrose JN. Perioperative immunotherapy with recombinant interleukin 2 in patients undergoing surgery for colorectal cancer. *Cancer Res* 1992; **52**: 5765–9.

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Review

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Quality-of-life measurement in surgical practice

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Assessment of quality of life is gaining momentum in areas of medical practice where standard measures of outcome are not sensitive enough to determine treatment strategies. Such methods have not been widely adopted in the surgical specialties, although this is changing. The techniques used are easily understood but they have not been standardized and are subject to several confounding factors. Nevertheless, quality-of-life measurement may provide additional information in the research environment and surgical audit.

Hippocrates[1] realized the importance of documenting all possible variations in each individual patient and then deducing their relevance:

> '... what food is given to him and who gives it ... the conditions of climate and locality both in general and in particular, the patient's customs, mode of life, pursuits and age ... his speech, his mannerisms, his silences, his thoughts, his habits of sleep or wakefulness and his dreams, their nature and time.'

Until recently, the results of treatment could be measured only in terms of death, disability or cure. Despite the increasing sophistication of new medical and surgical treatments, most surgical remedies are not measurable accurately in terms of survival; remarkably little attention has been given to establishing other means of measuring the effect of treatment. The dissatisfaction of some patients with conventional medicine is demonstrated by the increasing demand for 'alternative' remedies and increasing litigiousness. The dilemma of how to allocate priority in a medical system with finite resources is becoming more pressing. This paper addresses the questions of how to judge which treatments are the best, and who should offer them, to whom and when?

Quality-of-life measurement

The physicist Lord Kelvin[2] (1824–1907) stated:

> 'When you can measure what you are speaking of and express it in terms of numbers you know something about it: when you cannot express it in terms of numbers your knowledge is of a meagre kind.'

The simplest definition of life divides it into two dimensions: quantity and quality[3]. Quantity is easy to define and measure but defining quality is an exacting philosophical exercise[4], quality in medical care no less so[5]. The term quality of life was first coined by John F. Kennedy's presidential commission[6], which set goals for the USA for the year 2000. Elkington referred to it as a goal aimed for by every physician for the patient[7], but the ethos was clearly embodied in the constitution of the World Health Organization in 1947 in which health is defined not only as the absence of infirmity, but also as a state of physical, social and mental well-being[8].

In the realms of chronic or incurable disease, it is accepted that factors more subtle than survival alone must be taken into account in assessing treatment. In 1949, the oncologist Karnofsky and colleague Burchenal developed the first measure of 'performance'[9], a ten-point scale spanning the extremes of physical dependency as related to nursing burden and measured by an observer. For many years this scale was used widely, but often indiscriminately or inappropriately. It was improved 20 years later by the Activities of Daily Living scale[10]. In the past two decades a profusion of scales and questionnaires (instruments) have been developed, primarily for the measurement of health in patients with cancer or chronic disease, and usually to compare treatments in the context of trials. The common goal is measurement but the construct being measured differs depending on the instrument.

The terminology that has evolved is sometimes confusing. Spitzer advises that 'health status' should be used to describe instruments that are applied primarily to healthy people, whereas quality of life be used for those that apply to the sick[11]. However, the terms tend to be used interchangeably and quality of life in current usage broadly encompasses all measurement, irrespective of health state.

A growing number of trials reported in the literature have incorporated some element of quality-of-life measurement. This may have more to do with the changing influence of social values on the medical profession than a sudden increase in new treatments or technologies. Between 1966 and 1970, four papers had quality of life in the title, although more may have embodied the concept; in the next 5 years there were 33 papers[12]. In 1980, Mosteller *et al.* reported that, of 132 trials related to cancer, the overwhelming majority reported outcome only in terms of survival or recurrence[13]. Bardelli and Saracci reviewed cancer trials from 1956 to 1976 and found that in fewer than 5 per cent was quality of life quantified; even then objective functional measures such as the Karnofsky index rather than subjective quality-of-life measures were used[14]. Quality of life has now been a separate keyword in the *Index Medicus* for 15 years. However, while publications may mention quality of life, in only a minority is it actually measured.

When to measure quality of life

Measurement of quality of life is used mainly to evaluate the process and outcome of treatment in the research context of cohort studies and randomized comparisons. In the former, particularly useful for a quick answer to a simple question, a score before treatment is compared with a single score, or series of scores, after treatment. For randomized comparisons the change in scores over time is compared for two or more treatment groups in the context of a trial designed and conducted in the usual manner.

Among early attempts to use patient-derived quality-of-life data was the study by Priestman and Baum, who reported the use of linear analogue self-assessment to measure the quality of life of patients with advanced breast cancer treated by chemotherapy; a reduction in tumour size was associated with improved scores[15]. In the 1980s, quality-of-life measurement

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was developed for a variety of chronic conditions other than cancer such as hypertension[16], inflammatory bowel disease[17] and rheumatic disease[18]. It is currently being used in an ever widening range of trials and clinical situations. Even appendicectomy, once cited as an instance where quality-of-life measurement is superfluous[19], is now, with the advance of laparoscopic surgery, a candidate for such assessment.

Instruments for measuring quality of life

The instruments that are used presently measure quality of life in either general terms or specific illnesses. Almost all are now self-assessment instruments, designed to remove the potential for observer bias. Poor observer–respondent correlation in health status and quality-of-life measurement is a well documented phenomenon[20–22], so only a compelling reason such as extreme youth should allow the assessment of a proxy or observer to have precedence over that of the subject.

Instruments consist of a variable number of domains, usually one to six, that contain or gather information focused on a particular aspect of health and quality of life. Ware defined five generic health concepts or dimensions: physical health, mental health, social functioning, role functioning and general health perceptions[3]. The Nottingham Health Profile, perhaps the best known quality-of-life questionnaire, includes six domains: emotional reactions, energy, pain, physical mobility, sleep, and social isolation[23].

Each domain of a quality-of-life instrument contains items that can be complete questions requiring a 'yes' or 'no' answer (dichotomous) or symptoms inviting the selection of a graded response on a scale. The latter can be categorical (e.g. 'very much', 'somewhat', 'a little', 'not at all') or in a visual analogue form in which a mark is made on a straight line that spans the extremities of a symptom. There is no evidence that a visual analogue scale is superior or inferior to a categorical scale, although the latter has been advocated for simplicity[24]; nor is there evidence that an odd or even number of categories is preferable[25], although more than five points are superfluous in a categorical system[26].

The final score depends on the format chosen. A categorical scale is usually given an ascending integer score corresponding to the severity with which the symptom or item is perceived (e.g. 0–4). Each item of a visual analogue scale is usually scored on a 10-cm line divided into ten portions: the distance of the patient's mark along the line is given a score 0–9 (or 1–10), again depending on severity. Scores for individual items are summed to produce a score for that domain, but in some measures, e.g. the Nottingham Health Profile, a weighting system is derived from extensive validation exercises so that a positive response for each item is multiplied by a factor before aggregation[23]. Summation of the scores from separate domains into a global quality-of-life score is a prevalent practice, but may detract from rather than add to the precision of the data[27,28].

The timeframe is the period which the respondent is asked to consider in forming a response. Some measures of quality of life leave the timeframe undefined; in others, patients may be asked to consider the previous day, week or month before responding[27]. The periodicity or variability of the condition will dictate the choice of timeframe; for certain instruments it is built into the instrument design, for instance a diary card.

Many factors have influenced the development of quality-of-life measures. Those in common usage have all been through a rigorous process of development involving item selection, reduction in item number, design of format, pretesting, reliability testing (for repeatability), responsiveness (comparison with the change in other parameters, e.g. objective toxicity) and validity[27,29]. Validation needs time and patient numbers. Manuals exist for the majority of well validated instruments, containing score ranges for specific patient populations on which validation was conducted.

Quality of life as a measure of utility

The term quality of life is sometimes confused with the quality-adjusted life year (QALY), a measure of utility. This area accounts, at least in part, for the increased interest in the subject and represents the attempts being made to find a common currency with which to compare, and ultimately cost, different health states and treatment interventions. A pioneer in this field is Torrance, who developed the model of the QALY[30]: a model of health/time is used, applying to healthcare the analysis of cost-effectiveness and cost–utility[31]. The denominator is a year; the numerator is a number between 0 (death) and 1 (optimum health). Torrance is careful to point out that in this model quality of life is health related, i.e. without the social or 'beyond the skin' considerations included in other quality-of-life constructs. Torrance defines utility as 'a cardinal measure of the strength of one's preference' and derives the term from the utility theory model for decision making in the face of uncertainty[32]. The utilities are measured for various states of disease or health in two ways: as determined by patients actually in that state and hypothetically by observers who have experience of dealing with that health state. Torrance proposes that the resulting numbers or QALYs be used in three ways: in clinical decision making, in group comparisons and in health policy formulation. The principle was seized on by health economists at an early stage but application of the utility theory to real life has resulted in some perverse consequences. For example, in the Oregon experiment local citizens who were canvassed in a telephone questionnaire and asked to rank some 2000 conditions in order of priority ranked cosmetic breast surgery higher than treatment for a compound femoral fracture[33]. Harris argues that QALYs are unjust because they value time lived instead of individual lives[34].

Measuring the results of surgery

Medical audit has three components: structure, process and outcome[35]. The measurement of the first two has so far been of interest primarily to non-surgical professionals. Surgical outcome has traditionally been evaluated according to two basic measurable parameters: mortality and morbidity. Bunker and Wennberg drew attention to the inappropriateness of using mortality data to measure certain aspects of surgery, pointing out that elective surgery is directed primarily to improvement in quality of life, i.e. the relief of disability, discomfort and disfigurement[36]. Goligher acknowledged that surgeons often adopt too simplistic an approach to the outcome of their efforts and are frequently content to judge results in terms of operative mortality rate, immediate operative morbidity rate and, in the case of operations for malignant disease, length of survival. Goligher advocated operation-specific assessment, using a specially formulated and searching questionnaire[37]. One of the first surgeons to attempt measurement of the functional results of operation was Visick, who conceded that adverse results may arise from gastric surgery and so devised a simple scale with which to take account of postoperative function[38]. Goligher *et al.* used this scale to assess their results in the first randomized study by surgeons[39].

Troidl *et al.* highlighted the importance of finding better techniques to allow surgeons to measure quality of life in a simple and practical way[40]. Like Ware[3] and Aaronson[27], Troidl *et al.* advocated the use of specifically designed questionnaires to assess the precise outcome of operation, together with more general quality-of-life measures. Using this approach, outcome was assessed in patients with gastric cancer undergoing total gastrectomy with oesophagojejunostomy or construction of a Hunt–Lawrence–Rodino pouch[41].

The role of psychological factors in the outcome of surgery has been extensively discussed in the literature. Most authors have used observer-assessment as well as self-assessment scales. The adverse psychological consequences of mastectomy were reported by Morris *et al.*[42] and in the following year by Maguire and colleagues[43]. Fallowfield *et al.*, in a prospective study of

101 patients randomized to receive mastectomy or breast-conserving surgery, found morbidity rates equally high in both groups, probably as a result of the cancer itself[44]. Hughson *et al.* measured the profound psychological impact of chemotherapy after mastectomy[45] and the lesser impact of radiotherapy[46]. In most of these studies assessment was made by trained interviewers as well as validated questionnaires. In 1988, Koivukangas and Koivukangas reported a study into the quality of life of patients undergoing surgery for infiltrative brain tumours; they started using the Karnofsky scale[9] and Glasgow Outcome Score[47] but developed their own scale, based mainly on semistructured interviews repeated at intervals from before treatment[48]. In a study of patients undergoing minor surgery, postoperative psychological questionnaire scores were significantly better than preoperative scores, more so for patients claiming an improvement as a result of surgery (S. C. A. Fraser *et al.*, unpublished results).

Perhaps the most significant impediment to the acceptance of quality-of-life measurement as a bona fide branch of research is that it is regarded as 'soft' science by those who are used to measuring phenomena under laboratory conditions[49]. Feinstein described the science of 'clinimetrics': arbitrary ratings, scales, indices, instruments or other expressions that have been created as measurements for clinical phenomena that cannot be expressed in the customary dimensions of laboratory data[50,51]. Examples are the Glasgow Coma Scale[52], the Apgar score[53], the tumour node metastasis staging system[54] and the Visick scale[38].

Troidl observed that clinicians prefer 'hard' data, even when these are irrelevant in measuring the outcome for a patient, and they ignore soft data, like pain, fatigue and quality of life[55]. Even data traditionally regarded as hard, such as Dukes' staging for colorectal cancer, can be heavily observer dependent and subject to considerable variation.

Quality-of-life measurement in surgical practice

There is now an expectation that surgeons undertake detailed measurement of the effect that their work has on individual patients and the population. In the UK the National Health Service reorganization into purchaser and provider units has enhanced this and health economists scrutinize every aspect of surgical provision. Surgical audit, hitherto performed at the discretion and pace of the surgeon, is now being established with specific funds allocated from the health budget. To develop this process, better measures of outcome and process must be found. If surgeons wish to measure their practice more accurately, they need to know more about the instruments that may help with this task.

There is evidence that surgeons are now more willing to employ quality of life to measure the results of their work. In 1987 only 3 per cent of trials reported in surgical journals mentioned quality of life[56]. Some 5 years later there are examples of studies measuring quality of life in neurosurgery[57–61], carotid endarterectomy[62], head and neck cancer[63,64], congenital heart disease[65–67], coronary artery and valve surgery[68–73], cardiac dysrhythmia surgery[74], heart transplantation[75,76], aortic aneurysm[77], oesophageal and gastrointestinal surgery[78–82], hepatobiliary surgery[83,84], liver transplantation[85,86], colorectal surgery[87–91], benign and malignant prostatic surgery[92,93], renal tract stones[94], gynaecological cancer[95] and early breast cancer[96].

Outcome

The usual measures of outcome after surgical admission for non-life-threatening conditions are gleaned in a busy outpatient clinic with the answer to the question 'How are you feeling now?', the presence of a healed wound and the absence of surgical complications. Perhaps quality-of-life measurement would give full and pertinent outcome data even if uncomplemented by any other measurements.

Information regarding the anticipated outcome of treatment has a long tradition in the surgical literature. A significant finding from some studies is that quality-of-life scores before treatment can predict outcome. Morris and Sherwood[97] measured the decline in quality of life in terminally ill patients. In a later study of patients with advanced breast cancer undergoing chemotherapy, no single factor before treatment predicted survival or response more accurately than initial quality-of-life scores[98]. In 131 patients with acute abdominal pain, health-related quality-of-life measurements alone were inferior to clinical judgement in predicting non-specific pain[99]. However, in the self-selected subgroup of patients who responded to postal questionnaires, continued perception of pain was associated with anxiety at all stages, irrespective of diagnosis. In a study of 57 patients undergoing minor surgery, patients claiming a poor outcome had significantly poorer psychological scores before treatment, whereas those claiming improved health had significantly worse preoperative global health scores (S. C. A. Fraser *et al.*, unpublished results). The commonsense view of these findings would be that a practised clinician can tell which patients will benefit from treatment. That this can be measured, however, may be of more than academic interest in future.

In the future, quality-of-life considerations may require more complete documentation and may be scrutinized more closely than was previously considered necessary. Surgeons should become familiar with the potential advantages and pitfalls of quality-of-life measurement if they wish to maximize their contribution to the task of evaluating the delivery of surgical care. The incorporation of quality-of-life measurement into clinical audit is technically feasible; it is one of the few ways in which treatment strategies can be evaluated other than by measures of survival, complications and activity.

Methodological considerations

Choice of instrument

In advocating the involvement of surgeons in instrument development, Troidl argued that domination of quality-of-life research by sociologists and epidemiologists resulted in instruments far removed from clinical reality and inadequate or unacceptable for clinical purposes[55]. However, both Ware[3] and Aaronson[27], while advising the use of a well validated general questionnaire, suggested that an additional specific questionnaire (validated or *ad hoc*) focusing on the condition being examined should be adapted from existing measures rather than attempting to reinvent the wheel. Therefore, *ad hoc* questionnaires should be simple and designed along the standard lines recommended by other authors[100,29]. Several authors caution against using unvalidated measures but all measures start off unvalidated, including the Visick scale[40]. A comprehensive review of quality-of-life instruments has been provided by Fallowfield[101].

Compliance

A methodological drawback of any study requiring subjects to complete questionnaires voluntarily is compliance; this is especially relevant for studies of patients who are basically physically well. Poor patient compliance is blamed for deficiencies in design or conduct of many studies, not just those involving quality-of-life measurement. However, in quality-of-life studies it is particularly important that good compliance is achieved to minimize volunteer bias, the effect of which may be difficult to quantify on the validity of a study's findings. A clinical or research assistant should be present to guide and encourage the completion of questionnaires. For postal questionnaires compliance is better if each missive is accompanied by a telephone call. It takes committed investigators to make a success of such studies[6].

An ethical problem arises in the pursuit of non-compliers. To pursue too assiduously may breach an ethical boundary and the researcher may then be interfering with the quality of life of the patient. Patients have a right not to comply. Such a situation calls for tact, discretion and persuasiveness on the part of any investigator, features often omitted in the discussion of methodological issues in quality-of-life research. In this respect such work has much in common with market research which, while a valued tool in a manufacturer's armamentarium, is subject to the vagaries of public opinion and individual mood.

Data processing

One problem is the deficiency of information on the best method of processing the enormous number of data that accrue from quality-of-life measurement. It should not be assumed that the quality-of-life scores of a given population are distributed normally and it is safest to analyse data non-parametrically. The appropriate statistical tests are therefore kept simple and suitable books and computer programs are widely available. Measurements are generally compared with a baseline value for that patient. Factors other than the construct under examination may cause a change in quality-of-life score (e.g. a recent bereavement) so, unless group numbers are large or specific additional measures are employed to filter out such confounding factors, multiple measurements must be made over a period of time. Some of the principles of quality-of-life data analysis have been described by Fayers and Jones[102] and in a recent review by Cox *et al.* some important statistical problems were addressed[28].

Future of quality-of-life measurement in surgical practice

There is no evidence that the treatment or management policies of those who do not conduct research into quality of life have been substantially altered by the results of those who do. For instance, amputation has been abandoned in favour of limb-sparing surgery for extremity sarcoma, despite evidence that quality of life is no better for patients having the limb-conserving procedure[103]. This may be due to ignorance of work on quality of life[55]. In plastic surgery, a specialty in which quality of life must be the major if not the only endpoint, no study in the decade up to 1990 measured quality of life as an endpoint[104]. There may also be a view that quality-of-life issues can be resolved without recourse to measurement, as illustrated by the expansion of laparoscopic surgery in the absence of qualitative measurements to confirm its supposed superiority over conventional surgery.

The two biggest influences on treatment strategy are the amount of available resources, and cultural and technological considerations. Ideally, quality-of-life data should be used to make impartial judgements leading to appropriate changes in treatment practice rather than to support prejudices. It is important that a uniform approach to the measurement of quality of life evolves, with well validated instruments and methodology. So far, in most studies, widely varying instruments and timeframes have been used. It has long been recognized by the pharmaceutical industry that an advantage such as fewer side-effects may be an important feature of a particular product. It is significant that, with the advance of the science of quality-of-life measurement, more pharmaceutical companies are measuring quality of life in commercially sponsored trials[105]. This adds weight to the argument for a uniform approach.

Minimally invasive surgery

Baum has argued consistently for the randomized trial, except in the rare instance of a 'quantum leap' in medical progress[106]. Minimally invasive surgery may in some respects be a quantum leap in contemporary surgical practice but in others it is an area well suited to quality-of-life research.

Laparoscopic cholecystectomy has become the norm in many centres, so the opportunity to conduct a randomized comparison measuring quality of life with that after conventional cholecystectomy has been lost. No clinician would wish to deny their patient the option of a less invasive procedure. Although there is anecdotal evidence that considerable morbidity may result from laparoscopic procedures, the mortality and morbidity rates in published studies compare favourably with those of open operation[107–109]. As judged by duration of hospital stay and postoperative discomfort, the technique is superior to open operation; quality-of-life measurement would appear to be superfluous.

However, in areas where minimally invasive surgery is technically more difficult and has less obvious benefits, quality-of-life measurement should be applied. For example, Mays *et al.* reported no difference in quality of life between patients having extracorporeal shockwave lithotripsy and those having the more invasive percutaneous therapy[94]. Neugebauer *et al.* have addressed the problem by measuring as many outcome indicators as possible, including quality of life, as their laparoscopic cholecystectomy programme accelerates[110]. It seems likely that accurate quality-of-life measurement will confirm the place of laparoscopic surgery and it may be more valuable to apply the techniques to the selection of patients for surgery, a topic on which there is no universal consensus[111].

Audit

With the delivery of healthcare in Europe and the USA becoming more consumer sensitive, there is recognition among surgeons that closer scrutiny of outcome is warranted and that the structure and process of the delivery of surgical services should be examined[112–114]. The Royal College of Surgeons of England has an audit unit working towards the standardization of data collection on process and mortality. A patient satisfaction study has been designed to assess the extent to which clinical treatment and outcome meet the patient's expectations[115]. Furthermore, at least one study has now gathered a large number of patients in whom the Nottingham Health Profile has been used to measure the outcome of cholecystectomy[116].

If the software currently being installed for surgical audit were to allow later inclusion of outcome measurement using quality of life, self-assessment questionnaires could form or even replace part of the process of surgical consultation, admission, discharge and follow-up. Information about the achievement of treatment objectives and the whole 'surgical experience', seen from the patient's viewpoint, is as yet uncharted territory.

The Meran consensus conference

In October 1989 a group of surgeons and quality-of-life methodologists met in Meran, Italy, to discuss the issues and formulate objectives and guidelines for quality-of-life measurement in surgical practice. The conference met in small multidisciplinary groups in the specialties of transplantation, thoracic, cardiovascular, trauma or orthopaedic, and abdominal surgery to select diseases for which formal quality-of-life assessment was a priority, to consider how useful such information was in deciding whether or not to operate, and to monitor or evaluate patient status. The important quality-of-life domains in each disease state were defined and the instruments reviewed; the results were presented by each group to a plenary session[117].

Some obstacles were recognized as preventing quality-of-life measurement being taken up widely by surgeons at present: the perception that such work generates soft or less respectable data, the view that clinical judgement of a given situation was likely to be more reliable than quality-of-life data, and the complaint that quality-of-life measurement would add significantly to already considerable workloads. Moreover, the sheer number of quality-of-life instruments without a definite 'gold standard' may act as a deterrent to their use, especially when evidence is lacking that the results of quality-of-life studies make any real difference to clinical practice.

Conclusions

Key studies of quality of life in surgery in the coming years may encourage further research[37]. Some pointers have emerged from studies reported so far: reliable data can be obtained with a general well validated measure and a simple specific measure; controls should be used where possible; statistical analysis should be by simple non-parametric methods; the quality of life of study patients before a procedure may have considerable bearing on quality-of-life measurements afterwards. All that is now needed is for more surgeons to explore this area of research.

References

1. Lloyd GER, ed. *Hippocratic Writings*. London: Pelican, 1978.
2. Duncan W. Caring or curing: conflicts of choice. *J R Soc Med* 1985; **78**: 526–35.
3. Ware JE. Standards for validating health measures: definition and content. *Journal of Chronic Diseases* 1987; **40**: 473–80.
4. Pirsig R. *Zen and the Art of Motorcycle Maintenance*. London: The Bodley Head, 1974.
5. Donabedian A. *The Definition of Quality and Approaches to its Assessment*. Ann Arbor, Michigan: Health Administration Press, 1980: 79–128.
6. Williams JI. Strategies for quality of life assessment – a methodologist's view. *Theoretical Surgery* 1991; **6**: 152–7.
7. Elkington JR. Medicine and the quality of life. *Ann Intern Med* 1966; **64**: 711–14.
8. World Health Organization. The constitution of the WHO. *WHO Chronicle* 1947; **1**: 29.
9. Karnofsky D, Burchenal J. The clinical evaluation of chemotherapeutic agents in cancer. In: Macleod C, ed. *Evaluation of Chemotherapeutic Agents*. New York: Columbia University Press, 1949: 191–205.
10. Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. *Gerontologist* 1970; **10**: 20–30.
11. Spitzer WO. State of science 1986: quality of life and functional status as target variables for research. *Journal of Chronic Diseases* 1987; **40**: 465–71.
12. Spitzer WO, Dobson AJ, Hall J *et al*. Measuring the quality of life of cancer patients. A concise QL-index for use by physicians. *Journal of Chronic Diseases* 1981; **34**: 585–97.
13. Mosteller F, Gilbert JP, McPeek B. Reporting standards and research strategies for controlled trials: agenda for the editor. *Controlled Clin Trials* 1980; **1**: 37–58.
14. Bardelli D, Saracci R. Measuring the quality of life in cancer clinical trials: a sample survey of published trials. *UICC (International Union Against Cancer) Technical Report* 1978; **36**: 75–94.
15. Priestman TJ, Baum M. Evaluation of quality of life in patients receiving treatment for advanced breast cancer. *Lancet* 1976; **i**: 899–901.
16. Bulpitt CJ, Fletcher AE. Quality of life in hypertensive patients on different anti-hypertensive treatments: rationale for methods employed in a multi-centre randomised controlled trial. *J Cardiovasc Pharmacol* 1985; **7**(Suppl): 137–45.
17. Guyatt G, Mitchell A, Irvine EJ *et al*. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989; **96**: 804–10.
18. Laing MH, Robb-Nicholson C. Health status and utility measurement viewed from the right brain: experience from the rheumatic diseases. *Journal of Chronic Diseases* 1987; **40**: 579–83.
19. Ebbs SR, Fallowfield LJ, Fraser SCA, Baum M. Treatment outcomes and quality of life. *Int J Technol Assess Health Care* 1989; **5**: 391–400.
20. Slevin ML, Plant H, Lynch D, Drinkwater J, Gregory WM. Who should measure quality of life, the doctor or the patient? *Br J Cancer* 1988; **57**: 109–12.
21. Brewster S, Newman J. Can knee replacements be assessed by post? *Health Trends* 1991; **23**: 113–14.
22. Epstein AM, Hall JA, Tognetti J, Son LH, Conant L. Using proxies to evaluate quality of life. *Med Care* 1989; **27**(Suppl): 91–8.
23. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. *J R Coll Gen Pract [Occas Pap]* 1985; **35**: 185–8.
24. McQuay HJ. Assessment of pain and effectiveness of treatment. In: Hopkins A, Costain D, eds. *Measuring the Outcomes of Medical Care*. London: Royal College of Physicians of London, 1990: 43–57.
25. Remington M, Tyere PJ, Newson-Smith J, Cichetti DV. Comparative reliability of categorical and analogue rating scales in the assessment of psychiatric symptomatology. *Psychol Med* 1979; **9**: 765–70.
26. Lissitz RW, Green SB. Effect of the number of scale points on reliability: a Monte Carlo approach. *J Appl Psychol* 1975; **60**: 10–13.
27. Aaronson NK. Quantitative issues in health-related quality of life assessment. *Health Policy* 1988; **10**: 217–30.
28. Cox DR, Fitzpatrick R, Fletcher AE, Gore SM, Spiegelhalter DJ, Jones DR. Quality of life assessment: can we keep it simple? *Journal of the Royal Statistical Society* 1992; **155**: 353–92.
29. Guyatt GH, Bombardier C, Tugwell PX. Measuring disease-specific quality of life in clinical trials. *Can Med Assoc J* 1986; **134**: 889–95.
30. Torrance GW. Health status index models: a unified mathematical view. *Management Science* 1976; **22**: 990–1001.
31. Torrance GW. Utility approach to measuring quality of life. *Journal of Chronic Diseases* 1987; **40**: 593–600.
32. Holloway CA. *Decision Making Under Uncertainty: Models and Choices*. Englewood Cliffs, New Jersey: Prentice-Hall, 1979.
33. Klein R. On the Oregon trail: rationing health care. *BMJ* 1991; **302**: 1–2.
34. Harris J. Life: quality, value and justice. *Health Policy* 1988; **10**: 259–66.
35. Donabedian A. *The Definition of Quality and Approaches to its Assessment*. Ann Arbor, Michigan: Health Administration Press, 1980: 3–76.
36. Bunker JP, Wennberg JE. Operation rates, mortality statistics and the quality of life. *N Engl J Med* 1973; **289**: 1249–51.
37. Goligher JC. Judging the quality of life after surgical operations. *Journal of Chronic Diseases* 1987; **40**: 631–3.
38. Visick AH. A study of the failures after gastrectomy. *Ann R Coll Surg Engl* 1948; **3**: 266.
39. Goligher JC, Pulvertaft CN, DeDombal FT. Five to eight year results of Leeds/York controlled trial of elective surgery for duodenal ulcer. *BMJ* 1968; **ii**: 781.
40. Troidl H, Kusche J, Vestweber K-H, Eypasch E, Koeppen L, Bouillon B. Quality of life: an important endpoint both in surgical practice and research. *Journal of Chronic Diseases* 1987; **40**: 523–8.
41. Troidl H, Kusche J, Vestweber KH, Eyspasch E, Maul U. Pouch *versus* esophagojejunostomy after total gastrectomy: a randomised controlled trial. *World J Surg* 1987; **11**: 699–712.
42. Morris T, Greer HS, White P. Psychological and social adjustment to mastectomy (a 2-year follow-up study). *Cancer* 1977; **40**: 2281–7.
43. Maguire GP, Lee EG, Bevington DJ *et al*. Psychiatric problems in the year after mastectomy. *BMJ* 1978; **i**: 963–5.
44. Fallowfield LJ, Baum M, Maguire GP. Effects of breast conservation on psychological morbidity associated with diagnosis and treatment of early breast cancer. *BMJ* 1986; **293**: 1331–4.
45. Hughson AVM, Cooper AF, McArdle CS, Smith DS. Psychological impact of adjuvant chemotherapy in the first two years after mastectomy. *BMJ* 1986; **293**: 1268–71.
46. Hughson AVM, Cooper AF, McArdle CS, Smith DS. Psychological effects of radiotherapy after mastectomy. *BMJ* 1987; **294**: 1515–17.
47. Jennett B. *High Technology Medicine: Benefits and Burdens*. Oxford: Oxford Medical Publications, 1986.
48. Koivukangas P, Koivukangas J. Role of quality of life in therapeutic strategies in brain tumours. *Health Policy* 1988; **10**: 241–57.
49. Feinstein AR. Clinical biostatistics XLI. Hard science, soft data, and the challenge of choosing clinical variables in research. *Clin Pharmacol Ther* 1977; **22**: 485–98.
50. Feinstein AR. *Clinimetrics*. Newhaven, Connecticut: Yale University Press, 1987.
51. Feinstein AR. Clinimetric perspectives. *Journal of Chronic Diseases* 1987; **6**: 635–40.
52. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet* 1974; **ii**: 81–4.
53. Apgar V. A proposal for a new method of evaluation of the newborn infant. *Anaesthesiology and Analgesia* 1953; **32**: 260–7.
54. American Joint Committee for Cancer. *Staging and End Results Reporting: Manual for Staging of Cancer*. Chicago, Illinois: American Cancer Society, 1977.
55. Troidl H. Quality of life: definition, conceptualisation and implications – a surgeon's view. *Theoretical Surgery* 1991; **6**: 138–42.

56. O'Young J, McPeek B. Quality of life variables in clinical trials. *Journal of Chronic Diseases* 1987; **40**: 513–22.
57. Schulte FJ, Matthes-Martin S, Zarbock G, Herrmann HD. Prognosis and quality of life following tumors in the pineal region in childhood. *Klin Padiatr* 1987; **199**: 429–39.
58. Bach M, Schramm J, Brock M. Quality of life and mortality following major neurosurgical interventions in advanced age. *Z Gerontol* 1988; **21**: 134–7.
59. Stewart-Amidei C, Penckofer S. Quality of life following cerebral bypass surgery. *J Neurosci Nurs* 1988; **20**: 50–7.
60. McKenna P, Willison JR, Lowe D, Neil-Dwyer G. Recovery after subarachnoid haemorrhage. *BMJ* 1989; **299**: 485–7.
61. Trojanowski T, Peszynski J, Turowski K *et al.* Quality of survival of patients with brain gliomas treated with postoperative CCNU and radiation therapy. *J Neurosurg* 1989; **70**: 18–23.
62. De Leo D, Serraiotto L, Pellegrini C, Magni G, Franceschi L, Deriu GP. Outcome from carotid endarterectomy. Neuropsychological performances, depressive symptoms and quality of life: 8-month follow-up. *Int J Psychiatry Med* 1987; **17**: 317–25.
63. Strauss RP. Psychosocial responses to oral and maxillofacial surgery for head and neck cancer. *J Oral Maxillofac Surg* 1989; **47**: 343–8.
64. Rathmell AJ, Ash DV, Howes M, Nicholls J. Assessing quality of life in patients treated for advanced head and neck cancer. *Clin Oncol* (*R Coll Radiol*) 1991; **3**: 10–16.
65. Shimada M, Tsunemoto M. Long-term (10 to 23 years) clinical evaluation of quality of life in patients following open heart repair of tetralogy of Fallot. *Kyobu Geka* 1990; **43**: 634–9.
66. Torii S, Suma K, Miyawaki F, Shiroma K, Inoue K. Postoperative long-term quality of life at present after total correction of tetralogy of Fallot. *Kyobu Geka* 1990; **43**: 620–4.
67. Aigueperse J, Marechal MC. Evaluation of the quality of life in adulthood of 158 patients surgically-treated for tetralogy of Fallot. *Arch Mal Coeur* 1991; **84**: 685–90.
68. Mayou R, Bryant B. Quality of life after coronary artery surgery. *Q J Med* 1987; **62**: 239–48.
69. Langeluddecke P, Fulcher G, Baird D, Hughes C, Tennant C. A prospective evaluation of the psychosocial effects of coronary artery bypass surgery. *J Psychosom Res* 1989; **33**: 37–45.
70. Rogers WJ, Coggin CJ, Gersh BJ *et al.* Ten-year follow-up of quality of life in patients randomized to receive medical therapy or coronary artery bypass graft surgery. The Coronary Artery Surgery Study (CASS). *Circulation* 1990; **82**: 1647–58.
71. Jenkins CD, Jono RT, Stanton BA, Stroup-Benham CA. The measurement of health-related quality of life: major dimensions identified by factor analysis. *Soc Sci Med* 1990; **31**: 925–31.
72. Caine N, Harrison SC, Sharples LD, Wallwork J. Prospective study of quality of life before and after coronary artery bypass grafting. *BMJ* 1991; **302**: 511–16.
73. Booth DC, Deupree RH, Hultgren HN, DeMaria AN, Scott SM, Luchi RJ. Quality of life after bypass surgery for unstable angina. 5-year follow-up results of a Veterans Affairs Cooperative Study. *Circulation* 1991; **83**: 87–95.
74. de Carvalho TA, Sosa E, Marcial MB *et al.* The quality of life of patients with cardiac arrhythmia undergoing surgical treatment. *Arq Bras Cardiol* 1989; **53**: 147–50.
75. Lawrence KS, Fricker FJ. Pediatric heart transplantation: quality of life. *J Heart Transplant* 1987; **6**: 329–33.
76. Mai FM, McKenzie FN, Kostuk WJ. Psychosocial adjustment and quality of life following heart transplantation. *Can J Psychiatry* 1990; **35**: 223–7.
77. Rohrer MJ, Cutler BS, Wheeler HB. Long-term survival and quality of life following ruptured abdominal aortic aneurysm. *Arch Surg* 1988; **123**: 1213–17.
78. Habu H, Saito N, Sato Y, Takeshita K, Sunagawa M, Endo M. Quality of postoperative life in gastric cancer patients seventy years of age and over. *Int Surg* 1988; **73**: 82–6.
79. Sakamoto K, Nakano G, Hashimoto I, Nagamachi Y. Potential usefulness of a physical activity index in the assessment of quality of life of patients after gastrointestinal surgery. *Acta Chirurgica Scandinavica* 1989; **155**: 305–12.
80. Roder JD, Herschbach P, Ritter M, Kohn MM, Sellschopp A, Siewert JR. The quality of life following esophagectomy. The results of a psychosocial study of 80 cancer patients. *Dtsch Med Wochenschr* 1990; **115**: 570–4.
81. Buhl K, Schlag P, Herfarth C. Quality of life and functional results following different types of resection for gastric carcinoma. *Eur J Surg Oncol* 1990; **16**: 404–9.
82. Noguchi Y, Baba M, Nakano S *et al.* Quality of life of patients after esophagectomy for esophageal cancer. *Nippon Geka Gakkai Zasshi* 1991; **92**: 281–7.
83. Spina G, Santambrogio R, Opocher E *et al.* Improved quality of life after distal splenorenal shunt. A prospective comparison with side-to-side portacaval shunt. *Ann Surg* 1988; **208**: 104–9.
84. Little JM, Wong KP. Palliation of malignant jaundice. *Aust N Z J Surg* 1991; **61**: 501–4.
85. Kober B, Kuchler T, Broelsch C, Kremer B, Henne-Bruns D. A psychological support concept and quality of life research in a liver transplantation program: an interdisciplinary multicenter study. *Psychother Psychosom* 1990; **54**: 117–31.
86. Tarter RE, Switala J, Arria A, Plail J, Van Thiel D. Quality of life before and after orthotopic hepatic transplantation. *Arch Intern Med* 1991; **51**: 1521–6.
87. Kennedy HJ. Quality of life in patients with an ileostomy. *International Disability Studies* 1988; **10**: 175–6.
88. Yasutomi M, Shindo K, Matsuda T *et al.* Rectal cancer therapy compatible with preservation of function. *Gan To Kagaku Ryoho* 1988; **15**: 2681–5.
89. Drossman DA, Patrick DL, Mitchell CM, Zagami EA, Appelbaum MI. Health-related quality of life in inflammatory bowel disease. Functional status and patient worries and concerns. *Dig Dis Sci* 1989; **34**: 1379–86.
90. Walsh RM, Aranha GV, Freeark RJ. Mortality and quality of life after total abdominal colectomy. *Arch Surg* 1990; **125**: 1564–6.
91. Anseline PF. Quality of life after restorative proctocolectomy. *Aust N Z J Surg* 1990; **60**: 683–8.
92. Fowler FJ Jr, Wennberg JE, Timothy RP, Barry MJ, Mulley AG Jr, Hanley D. Symptom status and quality of life following prostatectomy. *JAMA* 1988; **259**: 3018–22.
93. Singer PA, Tasch ES, Stocking C, Rubin S, Siegler M. Sex or survival: trade-offs between quality and quantity of life. *J Clin Oncol* 1991; **9**: 328–34.
94. Mays NB, Petruckevitch A, Snowdon C. Patients' quality of life following extracorporeal shock-wave lithotripsy and percutaneous nephrolithotomy for renal calculi. *Int J Technol Assess Health Care* 1990; **6**: 633–42.
95. Sichel MP. Quality of life and gynecological cancers. *Eur J Gynaecol Oncol* 1990; **11**: 485–8.
96. Ganz PA, Schag CA, Cheng HL. Assessing the quality of life – a study in newly-diagnosed breast cancer patients. *J Clin Epidemiol* 1990; **43**: 75–86.
97. Morris JN, Sherwood S. Quality of life of cancer patients at different stages in the disease trajectory. *Journal of Chronic Diseases* 1987; **40**: 545–53.
98. Fraser SCA, Ramirez A, Ebbs SR *et al.* A daily diary for quality of life measurement in advanced breast cancer trials. *Br J Cancer* 1993 (in press).
99. Fraser SCA, Smith K, Agarwal M, Bates T. Psychological screening for non-specific abdominal pain. *Br J Surg* 1992; **79**: 1369–71.
100. Fitzpatrick R. Measurement of patient satisfaction. In: Hopkins A, Costain D, eds. *Measuring the Outcomes of Medical Care*. London: Royal College of Physicians of London, 1990: 19–26.
101. Fallowfield LJ. *The Quality of Life – The Missing Measurement in Health Care*. London: Souvenir Press, 1990.
102. Fayers PM, Jones DR. Measuring and analysing quality of life in cancer clinical trials: a review. *Stat Med* 1983; **2**: 429–46.
103. Sugarbaker PH, Barofsky I, Rosenberg SA, Gianola FJ. Quality of life assessment of patients in extremity sarcoma clinical trial. *Surgery* 1982; **91**: 17–23.
104. Spilker G, Stark GB. Quality of life considerations in plastic and reconstructive surgery. *Theoretical Surgery* 1991; **6**: 216–20.
105. Luce BR, Weschler JM, Underwood C. The use of quality of life measures in the private sector. In: Mosteller F, Falotico-Taylor J, eds. *Quality of Life and Technology Assessment*. Washington, DC: National Academy Press, 1989.
106. Baum M. Rationalism *versus* irrationalism in the care of the sick: science *versus* the absurd. *Med J Aust* 1989; **151**: 607–8.
107. Rees BI, William HR. Laparoscopic cholecystectomy: the first 155 patients. *Ann R Coll Surg Engl* 1992; **74**: 233–6.
108. Scott ADN, Greville AC, McMillan L, Wellwood JMcK. Laparoscopic laser cholecystectomy: results of the technique in 210 patients. *Ann R Coll Surg Engl* 1992; **74**: 237–41.
109. Hershman MJ, Rosin RD. Laparoscopic laser cholecystectomy: our first 200 patients. *Ann R Coll Surg Engl* 1992; **74**: 242–7.
110. Neugebauer E, Troidl H, Spangenberger W, Dietrich A, Lefering R and The Cholecystectomy Study Group. Conventional *versus* laparoscopic cholecystectomy and the randomized controlled trial. *Br J Surg* 1991; **78**: 150–4.

111. Scott EA, Black N. Appropriateness of cholecystectomy: the public and private sectors compared. *Ann R Coll Surg Engl* 1992; **74**(Suppl): 97–101.
112. Bates T. Avoiding inappropriate surgery: a discussion paper. *J R Soc Med* 1990; **83**: 176–8.
113. Kettlewell MGW. Surgical audit. *Ann R Coll Surg Engl* 1990; **72**(Suppl): 70–1.
114. Ellis BW. Surgical workload: variation in throughput. *Ann R Coll Surg Engl* 1991; **73**(Suppl): 72–4.
115. Meredith P. Audit and the quality of clinical care: patient satisfaction. *Ann R Coll Surg Engl* 1991; **73**(Suppl): 51–4.
116. Coles J. Outcomes, management and performance indicators. In: Hopkins A, Costain D, eds. *Measuring the Outcomes of Medical Care*. London: Royal College of Physicians of London, 1990.
117. Neugebauer E, Troidl H, Wood-Dauphinee S, Eypasch E, Bullinger M. Quality of life assessment in surgery: results of the Meran Consensus Development Conference. *Theoretical Surgery* 1991; **6**: 123–37.

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Announcement

The Halo Trust

The problem of mines mutilating and killing civilians decades after the conflict which spawned them has ended is now a fact of life for many countries throughout the world. The Halo Trust is a British charity that supervises mine-clearing teams in developing countries that do not have the resources for what is an extremely expensive and dangerous undertaking. They are currently working in Afghanistan and from April 1993 require doctors who are experienced in dealing with trauma. Travel expenses and a small honorarium are paid for periods of 1 month or longer. The job, which involves being available to deal with blast injuries as well as teaching health workers and helping in the local hospital, is generally regarded as a thoroughly satisfying experience. Anyone interested should ring 071 821 9244.

P. Hall

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Carotid endarterectomy improves haemodynamics on the contralateral side: implications for operating contralateral to an occluded carotid artery

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The importance of the patency of the contralateral carotid artery on the haemodynamic effect of a carotid stenosis was investigated. The breath-holding index was used to estimate cerebral perfusion reserve. The percentage rise in middle cerebral blood flow velocity, measured by transcranial Doppler ultrasonography, occurring during breath-holding was divided by the time of breath-holding. In study 1, ten subjects with no carotid stenosis, 13 with unilateral and eight with bilateral stenosis were studied. For unilateral stenosis the breath-holding index was reduced on the stenosed side compared with normal (0·85 versus *1·34 per cent per s,* $P < 0{\cdot}05$*). For bilateral disease, in the presence of severe stenosis on the side contralateral to that being examined, even a moderate stenosis (30–50 per cent) resulted in a much greater reduction in the breath-holding index. In study 2, the breath-holding index was measured before and after carotid endarterectomy in ten patients. The index increased significantly following operation, not only on the operated side (1·31* versus *0·79 per cent per s,* $P < 0{\cdot}01$*), but also on the contralateral side (1·23* versus *0·87 per cent per s,* $P < 0{\cdot}05$*). In three of four patients with contralateral stenosis >90 per cent or occlusion, operation improved the breath-holding index markedly (>90 per cent) on the non-operated side above the stenosis or occlusion. These results demonstrate the importance of patency of the contralateral carotid artery in determining the haemodynamic effect of a carotid stenosis. In addition, operating contralateral to an occlusion may improve haemodynamic status above the occlusion. Implications in selecting patients for carotid endarterectomy are discussed.*

Carotid endarterectomy reduces the risk of stroke in patients with a symptomatic carotid artery stenosis of $\geqslant 70$ per cent diameter[1,2]. Current opinion favours embolism from the carotid lesion as the major mechanism underlying stroke in these patients. However, an interesting point to emerge from carotid endarterectomy trials was that, in medically treated patients, there was a steadily increasing stroke rate with increasing degree of carotid stenosis, even above 70 per cent[1]. This suggests that haemodynamic factors may be important. The haemodynamic effect of a carotid stenosis depends not only on the degree of stenosis, but also on collateral supply. This includes the supply via the circle of Willis from the contralateral internal carotid artery. Collateral supply from the contralateral side will be important in determining the effect of any temporary reduction in flow above a carotid artery. Therefore, it is likely that the risk of stroke associated with a carotid stenosis will be increased in the presence of contralateral carotid disease.

One method of assessing cerebral haemodynamic status is to measure cerebrovascular reserve. In normal individuals a fall in perfusion pressure is counterbalanced by vasodilatation of cerebral arterioles; under normal conditions this mechanism maintains adequate cerebral blood flow. This cerebrovascular reserve can be estimated by measuring the change in cerebral blood flow that occurs in response to the vasodilator carbon dioxide. A proportion of individuals with occlusive carotid artery disease show reduced cerebrovascular reactivity as measured by this technique[3]. It is believed that haemodynamically compromised tissue is supplied by maximally, or near maximally, dilated arterioles, which are therefore unable to dilate much further in response to additional vasodilatory stimuli. Changes in cerebral blood flow can be estimated by using transcranial Doppler ultrasonography to measure changes in mean middle cerebral artery blood flow velocity (V_{mca})[4].

In this study cerebral reactivity measurements have been used to assess the effect of contralateral carotid occlusive disease on the haemodynamic effect of a carotid stenosis. This technique has also been used to assess the haemodynamic changes that follow carotid endarterectomy.

Patients and methods

Cerebral blood velocity was measured using a transcranial Doppler ultrasonographic velocimeter TC2-64B (EME, Uberlingen, Germany) fitted with a 2-MHz probe. The middle cerebral artery was insonated via the transtemporal window at a depth of 50 or 55 mm. The probe was held in place by an elasticated strap. The stimulus used to induce vasodilatation was breath-holding, which results in a rise in the arterial partial pressure of carbon dioxide. Reactivity assessed by this method has been shown to correlate with that measured using the administration of carbon dioxide[5]. Subjects were instructed to hold their breath after a normal inspiratory breath and the rise in V_{mca} was recorded. A deep breath was avoided as this induces a Valsalva effect which reduces V_{mca}; in contrast, breath-holding after a normal

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inspiratory breath results in neither a Valsalva effect nor an initial drop in arterial pressure and cerebral blood flow velocity[5]. The percentage rise in V_{mca} occurring during breath-holding was divided by the time of breath-holding in seconds to obtain the breath-holding index. Two measurements were made, separated by 2 min, and the mean taken.

Study 1

Patients were studied who presented with symptoms or signs suggestive of carotid territory ischaemia, and who had undergone high-resolution intravenous digital subtraction angiography (DSA) of the carotid arteries. They were divided into three groups according to the degree of ipsilateral and contralateral carotid stenosis: (1) no stenosis on either side; (2) unilateral stenosis (>30 per cent diameter) with normal contralateral carotid artery; and (3) bilateral stenosis (>30 per cent diameter stenosis on one side with a severe stenosis (90 per cent) or occlusion on the contralateral side).

The breath-holding index was measured on both sides in each subject.

Study 2

Patients who underwent carotid endarterectomy were studied. The breath-holding index was measured in the week before, and 1 month after, the operation.

Statistics

Comparisons between groups were made using Student's *t* test. $P < 0.05$ was considered significant.

Results

Study 1

There were a total of 31 patients in the three groups. Group 1 consisted of ten patients (three women) with a mean(s.d.) age of 63·1(10·3) years. The 13 patients (three women) in group 2 had a mean(s.d.) age of 64·7(9·4) years; on the affected side the mean(s.d.) degree of carotid stenosis was 70·0(20·1) per cent. The eight patients in group 3 were all men, with a mean(s.d.) age of 64·8(10·0) years. On the severely stenosed side in six patients in group 3 there was complete occlusion; in two there was 90 per cent stenosis. On the less affected side the mean(s.d.) degree of stenosis was 58·0(20·7) per cent.

The mean resting V_{mca} and breath-holding indices in the three groups of patients are shown in *Table 1*. Values for individual middle cerebral arteries are shown in *Figure 1*. The breath-holding index was reduced by 37 per cent on the side of stenosis in unilateral disease compared with normal ($P < 0.05$), while on the non-stenosed side it was the same as normal. However, in bilateral disease there was a much greater reduction in the breath-holding index, both on the more stenosed side (73 per cent reduction *versus* normal, $P < 0.0001$) and on the less stenosed side (56 per cent reduction *versus* normal, $P < 0.005$). In contrast, the mean values of resting V_{mca} were similar in all groups except on the severely stenosed side in bilateral disease where it was reduced by 17 per cent compared with normal ($P < 0.05$).

In the group with unilateral disease, five patients had a carotid stenosis in the range of 35–50 per cent, while in the group with bilateral disease six had a stenosis in this range on the less affected side. Comparison of the breath-holding index in these two subgroups revealed that it was lower in the group with bilateral disease (0·61 *versus* 1·21 per cent per s, $P < 0.05$), while the degree of carotid stenosis in the two groups was similar (46·7 *versus* 48·0 per cent).

Table 1 *Middle cerebral artery flow velocity and breath-holding index in three groups of patients with differing degrees of carotid disease*

	V_{mca} (cm/s)	Breath-holding index (% per s)
Normal	46·8(7·4)	1·34(0·65)
Unilateral disease		
Affected side	49·2(12·9)	0·85(0·48)*
Unaffected side	47·9(11·6)	1·34(0·50)
Bilateral disease		
More stenosed side	38·7(9·3)*	0·36(0·30)‡
Less stenosed side	53·2(10·8)	0·59(0·34)†

Values are mean(s.d.). V_{mca}, middle cerebral artery flow velocity. *$P < 0.05$; †$P < 0.005$; ‡$P < 0.0001$ (*versus* normal, Student's *t* test)

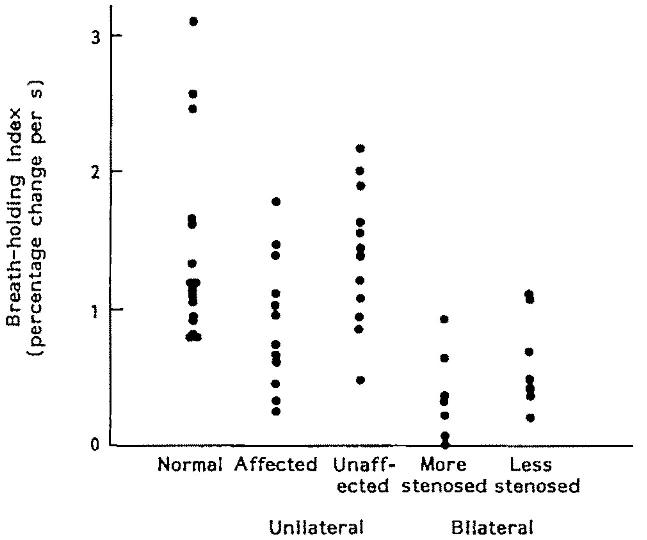

Figure 1 *Cerebral reactivity as measured by the breath-holding index in normal controls and patients with unilateral and bilateral carotid stenosis*

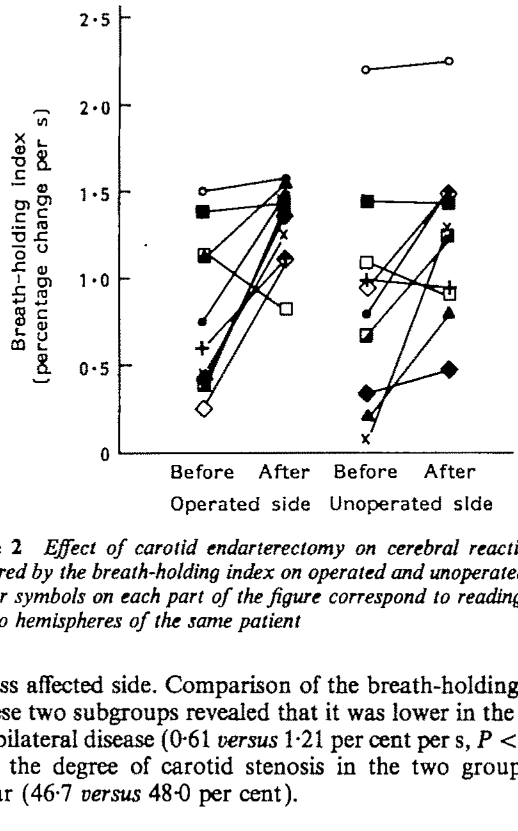

Figure 2 *Effect of carotid endarterectomy on cerebral reactivity as measured by the breath-holding index on operated and unoperated sides. Similar symbols on each part of the figure correspond to readings from the two hemispheres of the same patient*

Study 2

Ten patients were studied before and after carotid endarterectomy. The mean(s.d.) age was 65·2(8·5) years; all were men. The mean degree of carotid stenosis was 60 (range 45–90) per cent on the operated side and 43 (range 0–100) per cent on the contralateral side. Patency on the operated side was confirmed at 6 weeks to 1 year after surgery in all patients (by intravenous DSA in three, carotid duplex scanning in six and at autopsy in one who died from myocardial infarction 2 months after operation).

Measurement of cerebral reactivity 1 month after operation demonstrated no significant change in resting V_{mca} on either the operated side (48·7 *versus* 45·9 cm/s) or the contralateral side (42·8 *versus* 45·3 cm/s). However, the mean(s.d.) breath-holding index increased after operation on both the operated side (0·79(0·45) *versus* 1·31(0·24) per cent per s, $P < 0.01$) and the contralateral side (0·87(0·63) *versus*

1·23(0·49) per cent per s, $P < 0{\cdot}05$). Values for individual patients are shown in *Figure 2*. Three patients had a complete occlusion contralateral to the operated side and one had an asymptomatic 90 per cent stenosis. Three of the four showed marked (>90 per cent) improvement in breath-holding index after surgery on the non-operated side, i.e. above the occlusion or tight stenosis. The absolute values of the breath-holding index before and after operation, respectively, for the three patients with occlusion and the one with 90 per cent stenosis were 0·65, 1·22; 0·33, 0·47; 0·07, 1·29; and 0·21, 0·79 per cent per s.

Discussion

The results of study 1 demonstrate the importance of collateral supply, in this case via the contralateral internal carotid artery, in determining the haemodynamic effect of a carotid stenosis. A contralateral carotid stenosis or occlusion increases the likelihood that a stenosis will be associated with reduced cerebral perfusion reserve. By contrast, most patients with only a unilateral stenosis show no reduction of cerebrovascular reactivity below the normal range. These results are consistent with those found using alternative methods of measuring cerebral blood flow. Brown *et al.* studied unilateral carotid occlusion using the intravenous xenon-133 technique to estimate cerebral blood flow; carbon dioxide was the vasodilatory stimulus[3]. They found that, although mean values of hemisphere reactivity were reduced when patients were compared as a group with a group of normal controls, in the majority of individuals reactivity above an occlusion was well preserved and within the normal range[3]. However, the presence of contralateral carotid stenosis or occlusion resulted in a much greater reduction in hemisphere reactivity.

Study 2 demonstrates that cerebral reactivity on the side of carotid endarterectomy returns to normal following the operation. This improvement in reactivity following carotid endarterectomy has previously been reported by Takagi *et al.*[6] using xenon to measure cerebral blood flow. However, the present results demonstrate in addition that contralateral reactivity also improves in a number of patients following carotid endarterectomy. This suggests that it is possible to improve perfusion reserve above an occluded carotid by operating on a contralateral stenosis.

These results have two implications. First, if haemodynamic factors are indeed important in stroke, the risk of ipsilateral stroke from a carotid stenosis is likely to be increased in the presence of contralateral carotid disease. There are few clinical data that address the natural history of carotid stenosis in the presence and absence of contralateral stenosis, but preliminary data (H. J. Barnett, unpublished results) from the medical arm of the North American Symptomatic Carotid Endarterectomy Trial have demonstrated an increased risk of stroke when contralateral disease is present, which is abolished following carotid endarterectomy. This implies that the degree of stenosis at which surgery confers a prognostic benefit, which current data suggest lies between 30 and 70 per cent[1,2], may be lower in the presence of contralateral carotid stenosis. The estimation of cerebral reactivity may be a useful determinant in the evaluation of patients for carotid endarterectomy. This will depend on whether impaired reactivity implies an increased risk of subsequent stroke. There has been little work done on this aspect; neither of the two recent trials of carotid endarterectomy[1,2] included measurement of cerebrovascular reactivity in the preoperative evaluation. However, a recent prospective study has shown that the risk of stroke ipsilateral to a carotid occlusion is significantly increased if ipsilateral cerebrovascular reactivity is reduced, compared with carotid occlusion with normal reactivity[7]. It is likely that a similar situation occurs above a tight carotid stenosis, but further studies of the significance of impaired reactivity are required before its measurement can be recommended as a routine part of preoperative evaluation.

The second implication of the present results is that operating contralateral to a carotid occlusion will improve perfusion reserve above the occlusion in a proportion of patients. In such circumstances endarterectomy may provide a therapeutic benefit by reducing low-flow symptoms above an occlusion. Further clinical trials are required to determine whether endarterectomy produces a significant reduction in stroke above the occlusion.

References

1. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high grade carotid stenosis. *N Engl J Med* 1991; **325**: 445–53.
2. European Carotid Surgery Trialists Collaborative Group. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. *Lancet* 1991; **337**: 1235–43.
3. Brown MM, Wade JPH, Bishop CCR, Ross-Russell RW. Reactivity of the cerebral circulation in patients with carotid occlusion. *J Neurol Neurosurg Psychiatry* 1986; **49**: 899–904.
4. Bishop CC, Powell S, Rutt D, Browse NL. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. *Stroke* 1986; **17**: 913–15.
5. Markus HS, Harrison MJ. Estimation of cerebrovascular reactivity using transcranial Doppler, including the use of breath-holding as the vasodilatory stimulus. *Stroke* 1992; **23**: 668–73.
6. Takagi Y, Hata T, Ishitobi K, Kitagawa Y. Cerebral blood flow and CO_2 reactivity before and after carotid endarterectomy. *Acta Neurol Scand* 1979; **60**(Suppl 71): 506–7.
7. Kleiser B, Widder B. Course of carotid artery occlusions with impaired cerebrovascular reactivity. *Stroke* 1992; **23**: 171–4.

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Prospective randomized comparison of *in situ* and reversed infrapopliteal vein grafts

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A three-centre prospective randomized trial was undertaken to compare the efficacy of in situ *and reversed saphenous vein grafts for long bypasses to tibial and peroneal arteries. Of 162 patients entered into the study, 82 received an* in situ *graft and 80 a reversed vein graft. All operations were for limb salvage and the two groups of patients were well matched for age, sex, incidence of diabetes, smoking habits and coronary artery disease. At a maximum follow-up of 3 years there were 48 primary graft failures: 19 in the* in situ *group and 29 in the reversed vein group. Of these, three* in situ *grafts and seven reversed grafts were salvaged by secondary intervention. Secondary cumulative patency rates calculated at 3 years after operation were 68 and 66 per cent respectively for* in situ *and reversed grafts* (P *not significant*). *Cumulative limb salvage rates were 78 per cent for* in situ *grafts and 87 per cent for reversed grafts* (P *not significant*). *Separate analysis of a subgroup with small veins* ($\leqslant$*3·5 mm minimum diameter*) *showed cumulative patency rates at 2 years of 74 per cent for* in situ *grafts and 60 per cent for reversed grafts* (P *not significant*). *These results indicate that for veins* $>$*3·5 mm in diameter the* in situ *and reversed techniques for operation are equally effective. Some doubt remains about the best way of using smaller veins; a large number of such veins need to be studied to resolve this question.*

It is an enigma of vascular surgery that, despite 50 years' experience of saphenous vein grafting for infrainguinal arterial disease, there is still no consensus about how the operation should be performed. During this time the supremacy of the saphenous vein over other available materials has become well established, but whether the vein should be excised and reversed or left *in situ* is a conundrum that so far remains unresolved. Both of these principal variations of technique have their strong advocates, and surgical opinion on the matter is divided.

The only valid method for comparing the two operations is by prospective randomized trial. In 1987 the results were published of such a trial to compare reversed and *in situ* vein grafts for femoropopliteal bypass, which demonstrated no significant difference in outcome between them[1]. That trial has been criticized for failing to address the more crucial issue of long bypasses to infrapopliteal vessels. It has been pointed out that the performance of prosthetic grafts to popliteal arteries approaches that of veins and that it would be unreasonable to expect a relatively marginal difference in performance, which might be anticipated between *in situ* and reversed vein grafts, to become apparent from such a trial. For the same reason it has been argued that it is unsafe to extrapolate the results to distal bypasses where the intrinsic properties of the conduits used are known to be rather more critical to the outcome. It was therefore necessary to undertake a new trial to compare the performance of *in situ* and reversed vein grafts to tibial, peroneal or pedal arteries[2]. Because of the relatively low incidence of these operations it was considered expedient to conduct this as a multicentre trial. Three centres with a good track record for distal bypass surgery have collaborated for this purpose: Montefiore Medical Centre, New York, USA; Broadgreen Hospital, Liverpool, UK; and St James's Hospital, Dublin, Ireland. The project was commenced in 1988 and the interim results with a maximum follow-up of 3 years after operation are reported.

Patients and methods

Patient population

Of 162 patients entered into the study, 82 were randomly allocated to receive an *In situ* graft and 80 a reversed vein graft. Approval for the study was granted by the respective institutional review boards and informed consent to randomization obtained from each patient. The proportion of *in situ* and reversed grafts was similar for all three participating centres. The characteristics of patients in the two groups are compared in *Table 1*, which shows that they were well matched for age, sex, incidence of diabetes, smoking habits and coronary artery disease.

The indications for surgery are shown in *Table 2*. More than 90 per cent of patients had critical lower-limb ischaemia with either rest pain of at least 4 weeks' duration or, in two-thirds, established tissue necrosis in the affected limb and a systolic blood pressure at the ankle <50 mmHg. In 9 per cent the indication for operation was disabling intermittent claudication with the addition, in most cases, of trophic changes or discomfort at rest, suggesting threatened limb viability but falling outside a strict definition of critical ischaemia. There was no significant difference in mode of presentation between the two groups of patients.

Operative technique

A standardized protocol was used in all three centres for both

Table 1 *Patient characteristics*

	In situ graft (n = 82)	Reversed graft (n = 80)	Total (n = 162)
Mean age (years)	73·9	71·8	72·8
Sex ratio (M:F) (%)	51:49	59:41	55:45
Diabetes (%)	51	60	56
Smoking (%)	51	47	49
Coronary artery disease (%)	40	49	45

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Table 2 *Percentage of patients undergoing primary and repeat operations and indications for surgery*

	In situ graft ($n = 82$)	Reversed graft ($n = 80$)	Total ($n = 162$)
Primary procedure	83	82	82
Previous operation	17	18	18
Indication			
Gangrene or ulceration	63	61	62
Rest pain	26	31	28
Other	11	8	9

operations. All patients were assessed before surgery by conventional or digitally enhanced angiography and by non-invasive laboratory studies. The course of the ipsilateral long saphenous vein was marked on the skin. In cases of doubt peroperative angiography was used to identify the most appropriate vessel and site for the distal anastomosis. Peroperative heparin anticoagulation was employed in all cases; platelet aggregation was suppressed with oral aspirin, commencing at least 48 h before operation and continued afterwards.

Reversed vein operation

The vein was exposed throughout its length by an incision made directly over it, allowing its removal with minimal manipulation. Care was taken not to pick the vein up or otherwise traumatize it with metal instruments, and the tributaries were ligated with fine silk ties placed 1–2 mm away from the main conduit to avoid adventitial tethering. The vein was gently distended with heparinized blood and its minimal diameter measured at this stage. It was placed in a deep tunnel alongside the natural artery but superficial to the adductor magnus tendon; in all cases the anastomoses were constructed in an end-to-side manner using fine vascular sutures with the aid of magnification as appropriate. Peroperative angiography to detect technical error was undertaken on completion of both anastomoses.

In situ *vein operation*

The vein was exposed throughout its length to identify any excessively narrow or phlebitic segments and permit ligation in continuity of all visible tributaries. The saphenofemoral junction was carefully dissected and divided with a side clamp applied to the common femoral vein. The resultant defect in the femoral vein was repaired with a continuous fine vascular suture. After excising the first valve under direct vision with fine scissors, the proximal anastomosis was fashioned in an end-to-side manner. If there was insufficient length of vein for direct anastomosis to the common femoral artery without tension, either the superficial femoral or profunda artery was used. With arterial pressure distending the vein and filling the valve cusps, either a Hall's or modified Mills' retrograde valvulotome was introduced from the distal end of the graft or via side branches, and each set of valve cusps disrupted in turn. Only small sizes of valvulotome (mostly 2·5 mm) were used, in an attempt to reduce the risk of endothelial trauma. Once pulsatile flow had been observed from the distal end of the graft, a soft microclip was applied and the distal anastomosis constructed in an end-to-side fashion. Completion angiography was used to identify undisrupted valve cusps, unligated tributaries and technical defects; this was repeated as necessary. After completion of the bypass the minimum diameter of the vein and its length were measured.

Follow-up

All grafts were subjected to postoperative surveillance programmes using duplex scanning to confirm patency and detect evidence of graft-related stenoses[3,4]. Early secondary intervention for stenoses that threatened graft patency was performed by either percutaneous balloon angioplasty or open surgery.

Results

The veins were similar in terms of length and minimum diameter in the two groups, as were the outflow conditions (*Table 3*).

Forty-eight primary graft failures with a maximum follow-up of 3 years have occurred to date, 19 in the *in situ* group and 29 in the reversed vein group. Of these, three *in situ* and seven reversed grafts were salvaged by secondary intervention. The secondary cumulative patency rates at 3 years after operation were 68 and 66 per cent respectively for *in situ* and reversed

Table 3 *Characteristics of grafts and details of outflow tracts*

	In situ graft	Reversed graft	Total
Mean graft length (cm)	64·5	60·2	62·5
Minimum graft diameter (mm)*			
>3·5	29	25	27
≤3·5	60	66	63
Not recorded	11	9	10
Outflow vessel*			
Tibioperoneal trunk	7	4	6
Anterior tibial	23	29	26
Posterior tibial	22	29	25
Peroneal	29	25	27
Dorsalis pedis	18	14	16
Run-off*			
Blind or distal occlusion	8	14	11
One patent vessel	56	62	59
More than one vessel	2	2	2
Not recorded	33	21	27

*Values are percentages

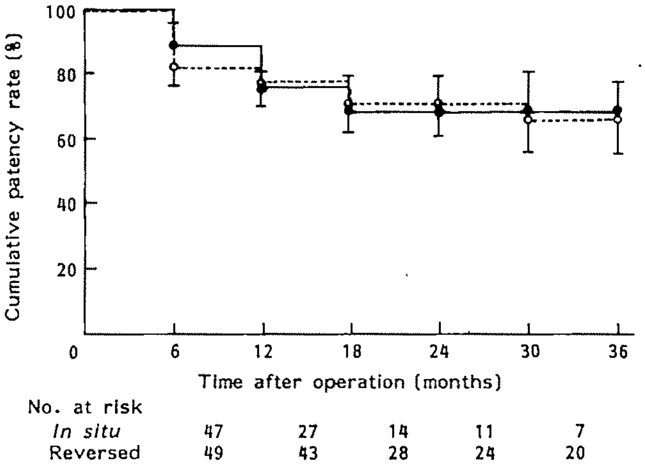

Figure 1 *Secondary cumulative patency rate in* in situ (●) *and reversed* (○) *vein grafts. Bars are s.e. There were no statistically significant differences at any stage up to 3 years after operation (log rank test)*

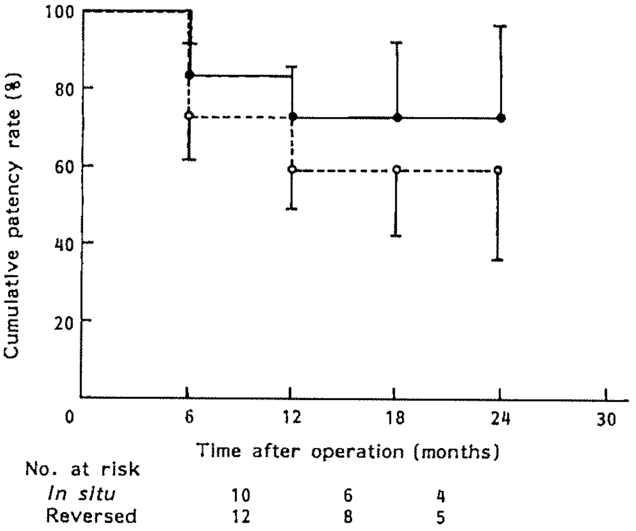

Figure 2 *Secondary cumulative patency rate in* in situ (●) *and reversed* (○) *vein grafts with a minimum diameter ≤3·5 mm. Bars are s.e. There were no statistically significant differences up to 2 years after operation (log rank test)*

grafts (*Figure 1*). Neither the primary nor secondary patency rates differed significantly between the two types of graft (log rank test).

Separate comparison by life-table analysis of small veins ($\leqslant$3·5 mm minimum diameter) showed a secondary patency rate at 2 years of 74 per cent for *in situ* grafts *versus* 60 per cent for reversed grafts (*Figure 2*). These rates were not significantly different (log rank test).

Graft failure usually resulted in limb loss. Limb salvage rates associated with *in situ* and reversed grafts were 78 and 87 per cent respectively (*P* not significant, log rank test).

Discussion

Over the years the relative popularity of the reversed and *in situ* vein graft operations has fluctuated considerably. Both techniques were conceived at about the same time, but the *in situ* operation was not widely practised until effective intraluminal valvulotomes became available. The reversed operation, as described by Kunlin[5] in 1949, was therefore the first to become established and remained largely unchallenged as the method of choice for the next 30 years. The *in situ* method found favour sporadically from the early 1960s[6], and gained substantial popularity in the late 1970s following reports of excellent results by Leather *et al.*[7,8].

For the past 10 years the *in situ* method has been on the ascendancy. Proponents of this technique cite a number of theoretical advantages in its favour. Unlike the reversed vein, which is removed completely from its vascular bed, the *in situ* vein remains substantially undisturbed without disruption of its vasa vasorum. In theory, therefore, the *in situ* vein has the potential to retain a viable endothelium from its inception as an arterial conduit. This thin monolayer of cells has hormonal and metabolic functions. It maintains a non-thrombogenic surface by producing prostacyclin, tissue plasminogen activator, antithrombotic cell surface proteins, heparin and endothelium-derived relaxing factor; it also exerts important vasomotor control. However, the complexity of this tissue is matched only by its delicacy; even minimal trauma, for example that inflicted by the passage of a valvulotome, easily removes it. When injured, the endothelium may become procoagulant, promoting platelet adhesion and activating the coagulation cascade. There is also evidence that endothelial injury and the associated interaction with platelets may initiate changes through the activation of smooth muscle cells, resulting in the later formation of myointimal stenoses. It is, however, a moot point whether these adverse effects of endothelial injury are more or less likely to occur if the vein is reversed than if it is left *in situ*.

Another stated benefit of the *in situ* vein graft is its natural taper. Most surgeons would accept that close matching for size between the graft and recipient artery is helpful in facilitating the anastomosis, but claims for increased haemodynamic efficiency related to the taper of an *in situ* bypass have not been substantiated by experimental studies.

The presence of valves in a reversed vein graft might inhibit natural blood flow reversal during diastole, and it is claimed that the absence of intact valves in an *in situ* graft may thereby confer haemodynamic advantages. If this were a significant factor, comparison of velocity waveforms between the two types of graft would be expected to show differences but, to date, objective evidence for this is lacking.

Finally, it has been asserted that veins that are too small to be reversed can be utilized effectively in the *in situ* technique[8]. However, this also has been challenged and there are those who contend that any vein that is suitable for *in situ* bypass can equally well be used in reversed fashion[9].

There are potentially rather more technical hazards associated with the *in situ* operation, and additional operative checks are required to ensure that all valve cusps and potential sources of arteriovenous fistula have been dealt with effectively, so prolonging the procedure appreciably[10]. For this reason many surgeons might have a preference for the technically more simple standard reversed vein operation, had they not been persuaded that its outcome in terms of graft patency was inferior to that of the *in situ* procedure.

In fact, most claims for superior patency associated with the *in situ* operation have been based almost entirely on credence given to the well recognized but largely unproven theoretical advantages outlined above, supported only by comparison with the results of non-contemporaneous series of reversed vein operations. The present study is the first prospective randomized comparison of the two procedures.

The results suggest that there is nothing to choose between *in situ* and reversed vein grafts for long femorodistal bypass grafting, and accord with the outcome of a previous trial showing equal patency for more proximal bypasses[1]. At face value these results suggest that surgeons might reasonably follow their own personal preference in the choice of technique for femoropopliteal or femorodistal vein graft operations. It is necessary, however, to consider the validity of such a conclusion carefully.

Proponents of either technique might claim that they are able to achieve superior results with their own preferred method to those reported here. Such comparisons are spurious and do not undermine the validity of the present study, which has been conducted according to a well accepted protocol of randomization to ensure that variable influences are equally balanced. The grafts were, therefore, similar in length and complexity; this is rarely, if ever, the case when non-randomized comparisons are made. The results could, in theory, have been skewed if the participating surgeons had been more skilled in one technique than the other; this is one factor that would not be compensated for by the design of the trial. Involvement of more than one centre minimizes such a risk and all three principal surgeons were very experienced with both techniques before the start of the study. It is unlikely that any bias of this nature has influenced the results.

The outcome from femorodistal bypass surgery is known to be influenced considerably by the selection criteria applied to patients and, in the case of vein bypass, by the criteria used to accept or reject the ipsilateral saphenous vein. On both counts all three participating surgeons exercised a very liberal policy. Patients were rejected for surgery only if moribund or if the limb was gangrenous beyond redemption, and so a substantial proportion of those accepted for operation were in a surgical high-risk category.

Some 14 per cent of veins were rejected at operation after randomization, a proportion that was similar in both groups. It was a deliberate policy to use all but the smallest diameter veins to examine the claim that small veins function more effectively and with better patency rates if used *in situ* than when reversed. Because there were relatively few veins in this category, this aspect of the study remains inconclusive. Although there was a trend in favour of the *in situ* method, this was not statistically significant and the results at this stage do not provide incontrovertible evidence for the superiority of the small-diameter *in situ* graft. The indications are that long vein grafts $\leqslant$3·5 mm in diameter have a very high failure rate whatever method of insertion is used, and there is a case for considering prosthetic alternatives in this situation.

Vein grafts are prone to develop stenosis during the first 6–9 months after implantation and this is the principal cause of failure during the first year[3]. Grafts in the present study were subjected to surveillance programmes to detect such lesions, and early secondary intervention undertaken as required[4]. The incidence, morphology and distribution of postoperative stenosis was not significantly different in the two types of graft, and both primary and secondary patency rates were similar. These findings do not provide support for the contention that the pathogenesis of postoperative stenosis in *in situ* and reversed vein grafts may be different.

After the first year, the patency rate of autologous vein grafts, both *in situ* and reversed, becomes relatively stable, with a low annual attrition rate of about 5 per cent caused mainly by progression of underlying arterial disease. All grafts included in this study remain under continued observation but, given the very closely matched patency rates after 2 years, it is unlikely that an overall statistically significant difference will appear beyond this time. The principal outstanding area of doubt concerns the best way of using small veins, i.e. those with a minimum diameter $\leqslant 3{\cdot}5$ mm. Resolution of this problem will require the accession of additional veins in this category and so recruitment into the trial is continuing.

The primary conclusion drawn from this study, that *in situ* and reversed vein grafts perform equally well in femorodistal bypass reconstructions, is valid only for situations in which the techniques are equally applicable, which is not always the case. Nor should the results be interpreted as lending support to those who are slavishly committed to one method in preference to the other, whatever the circumstances. On the contrary, the results suggest that flexibility in distal bypass surgery is the most sensible approach. Of the two methods, the reversed operation is the more versatile, in that veins of the best quality can be selected and positioned for maximal effect; it is also less time consuming than the *in situ* method. Graft failure increases with the length of the bypass, and the chances of patency may be improved in selected cases by using a distal inflow site[11]. It has been demonstrated that smaller diameter veins (2–3 mm) can be used successfully in the reversed technique in this way[12]. There may be instances in which the *in situ* method is technically easier or otherwise more appropriate. Other options that have not been assessed in this trial are composite grafts and non-reversed transposed vein grafts. Proponents of the latter method claim that it combines the advantages of both the *in situ* and reversed operations[13], but it may equally be said to retain some of their disadvantages. The essential principle seems to be that vein graft operations should be tailored according to circumstances, and there are claims that, by careful application of such a policy, fewer than 1 per cent of veins are totally unusable.

The results of this trial, in conjunction with the excellent findings reported previously by proponents of both main variations of technique, suggest that factors such as astute patient selection, careful siting of the anastomosis, respectful handling of the graft, accurate suturing and effective quality control may be more important to a successful outcome than whether the vein is *in situ* or reversed. Excessive adherence to one favoured method could be counterproductive. A flexible individualized approach is advocated but, where *in situ* and reversed vein grafts are equally applicable, the choice may reasonably be determined by the surgeon's idiosyncratic preference.

References

1. Harris PL, How TV, Jones DR. Prospectively randomized clinical trial to compare *in situ* and reversed saphenous vein grafts for femoropopliteal bypass. *Br J Surg* 1987; **74**: 252–5.
2. Wengerter KR, Veith FJ, Gupta SK *et al.* Prospective randomised multicentre comparison of *in-situ* and reversed vein infrapopliteal bypass. *J Vasc Surg* 1991; **13**: 189–99.
3. Grigg MJ, Nicolaides AN, Wolfe JHN. Femorodistal vein bypass graft stenoses. *Br J Surg* 1988; **75**: 737–40.
4. Moody P, Gould DA, Harris PL. Vein graft surveillance improves patency in femoro-popliteal bypass. *Eur J Vasc Surg* 1990; **4**: 117–21.
5. Kunlin J. Le traitment de l'arterite obliterante par la greffe veineuse. *Archives Chirurgie Mal Coeur* 1949; **42**: 371–2.
6. Hall KV. The great saphenous vein used '*in situ*' as an arterial shunt after extirpation of the vein valves. *Surgery* 1962; **51**: 492–5.
7. Leather RP, Powers SR, Karmody AM. A re-appraisal of the *in-situ* saphenous vein arterial bypass. Its use in limb salvage. *Surgery* 1979; **86**: 453–61.
8. Leather RP, Shah DM, Karmody AM. Infrapopliteal arterial bypass for limb salvage: increased patency and utilisation of the saphenous vein used '*in-situ*'. *Surgery* 1981; **90**: 1000–8.
9. Porter JM. *In situ versus* reversed vein graft: is one superior? *J Vasc Surg* 1988; **7**: 79–80.
10. Cave-Bigley DJ, Ackroyd N, Campbell H, Harris PL, Parry EW. Technical problems associated with *in situ* vein grafts. *Br J Surg* 1984; **71**: 211–13.
11. Veith FJ, Gupta SK, Samson RH. Superficial femoral and popliteal arteries as inflow sites for distal bypasses. *Surgery* 1981; **90**: 980–90.
12. Veith FJ, Ascer E, Gupta SK. Tibio-tibial vein bypass grafts: a new operation for limb salvage. *J Vasc Surg* 1985; **2**: 552–7.
13. Beard JD, Wyatt MG, Scott DJA, Poskitt KR, Horrocks M. The non-reversed femoro-distal bypass graft: a modification of the standard technique. *Eur J Vasc Surg* 1989; **3**: 55–60.

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Critical leg ischaemia: an appraisal of clinical definitions

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The reliable prediction of imminent limb death remains a clinical problem. The International Vascular Symposium and European working parties each produced similar definitions of 'critical ischaemia', but this is the first attempt to address the issue with prospectively collected data. Complete 3-year follow-up data were available for 213 patients. In addition to the above two definitions, a simplified modification has been evaluated, after review of the data 1 year into this study. All three definitions were able to identify patients likely to require amputation in the absence of successful reconstruction. The sensitivity, specificity and positive predictive values with which they were able to do so was, however, poor. None of the definitions was able to predict which diabetic patients would require amputation. Diabetics were more likely to undergo amputation than non-diabetics. There was, however, no significant difference in the initial ankle artery pressures between the diabetic and non-diabetic patient subgroups. None of the definitions reliably predicted which grafts would occlude, in which event the 3-year mortality rate was approximately 35 per cent. Critical ischaemia by any of these definitions is associated with a high mortality rate. Arterial reconstruction is associated with a reduction in both mortality and amputation rates These data do not support the hypothesis that critical ischaemia is associated with a greater graft occlusion rate than lesser degrees of severe ischaemia.

There is wide variation in the published results of arterial reconstructive surgery. This is usually ascribed to differences in patient selection rather than to variations in surgical technique. An attitude of therapeutic nihilism and cynicism regarding data from any centre reporting better than average results has ensued. This attitude is supported by a widespread presumption that patients undergoing surgery for claudication are more likely to have prolonged graft patency than similar patients undergoing the same procedures for 'limb salvage'. Unfortunately, the term limb salvage lacks formal clinical definition and has often been inappropriately applied, which has hindered corroboration of this hypothesis.

In an attempt to reduce future ambiguity, the International Vascular Symposium (IVS) working party suggested the term 'critical ischaemia' (*Table 1*)[1]. Since the original IVS definition, the authors have proposed modifications of these clinical criteria on the basis of a 1-year follow-up of the patients in this study[2]. More recently, the European Working Group on Critical Limb Ischaemia has produced a further definition[3]. There is, however, little prospective evidence to support the validity of any clinical definition in predicting the need for amputation in the absence of successful vascular surgical intervention.

In addition to clarifying the reasons for the variation in clinical results reported, a meaningful clinical definition of critical ischaemia may aid clinical decision making. In particular, legs satisfying such a definition should fulfil an absolute indication for either arterial reconstruction or amputation.

Patient data from nine UK centres were gathered prospectively and the original IVS working party definition and its two modifications applied to assess their capacity to predict mortality and amputation rates, and the likelihood of graft occlusion, within 3 years of the initial assessment.

Patients and methods

The Joint Vascular Research Group at the time constituted 16 UK vascular surgeons representing both district and university hospitals. Nine centres contributed patient data for the purpose of this study.

A total of 411 consecutive patients with a clinical diagnosis of critical ischaemia were entered into the study over 8 months during 1984. Demographic data concerning age, previous vascular history, risk factors for atheroma (including the presence or absence of diabetes) and presenting complaint were recorded on admission, as were the results of routine blood tests and angiography. All patients had Doppler ankle artery pressures measured and the presence of ischaemic ulceration or gangrene was noted. A record of the management and early (30-day) outcome was kept. Patients were followed at intervals of 3 months for the first year, and the data collated. A 3-year follow-up was performed by the surgical team concerned wherever possible, but also involved correspondence with the patient's general practitioner. Only patients with a complete data record for the 3 years have been included in the present analysis.

Table 1 *Definitions of critical ischaemia*

International Vascular Symposium working party definition
1. Severe rest pain requiring opiate analgesia for at least 4 weeks
   and either:
2. Ankle artery pressure <40 mmHg
   or:
3. Ankle artery pressure <60 mmHg in the presence of tissue necrosis or digital gangrene

(Diabetics should be excluded from the ideal clinical study.)

Modified International Vascular Symposium working party definition
1. Severe rest pain requiring opiate analgesia for at least 4 weeks
   and either:
2. Ankle artery pressure <40 mmHg
   or:
3. Tissue necrosis or digital gangrene

European Working Group definition
1. Severe rest pain requiring opiate analgesia for at least 2 weeks
   or:
2. Ulceration or gangrene
   and:
3. Ankle artery pressure <50 mmHg

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The data were then categorized according to the original IVS definition of critical ischaemia, according to the modification suggested by the present authors, and according to the European Working Group on Critical Limb Ischaemia definition (*Table 1*); outcome in terms of graft patency, amputation and mortality rates was examined. Statistical analysis was performed using χ^2 or Fisher's exact test according to the number of patients involved.

Results

Sufficient data were available for this analysis from 213 of the 411 patients initially entered. The median age of this group was 67 years and the male:female ratio 2·4:1. A total of 35 patients (16 per cent) had diabetes.

During initial admission, 144 patients (68 per cent) had a total of 147 arterial reconstructions (36 suprainguinal, 92 infrainguinal, 13 combined segment, three balloon dilatation alone, three balloon dilatation together with surgical reconstruction); 69 patients (32 per cent) did not undergo arterial reconstruction, of whom 27 underwent major primary amputation and 42 lumbar sympathectomy or medical treatment (usually drug infusion).

At 3 years, 72 patients (34 per cent) had died: 12 during initial admission, 33 between discharge and the end of the first year, and 27 after the first year. A total of 76 amputations (36 per cent) had been performed: 36 during initial admission, 24 between discharge and the end of the first year, and 16 after the first year.

Of the 144 patients undergoing reconstructive procedures, 54 grafts (37 per cent) in 51 legs occluded (seven suprainguinal, 41 infrainguinal, three combined segment) within the 3-year follow-up period. Occlusion was treated by amputation in 39 patients, and was associated with a 31 per cent mortality rate within the 3-year follow-up period.

Twenty-seven patients were treated by primary amputation; 14 had died at the completion of follow-up. Of the 42 patients treated by lumbar sympathectomy or medical management, 22 had died within the 3-year follow-up and ten had come to amputation. By contrast, of the 144 patients in whom reconstructive techniques were attempted, 36 (25 per cent) had died ($P < 0·0001$) and 38 (26 per cent) had required amputation ($P < 0·0001$) within the 3-year follow-up. In addition, primary amputation was associated with a higher mortality rate than attempted revascularization ($P < 0·005$). Diabetic patients had a higher risk of amputation (54 per cent) than non-diabetics (32 per cent) ($P < 0·01$) but were no more likely to die.

Peak systolic Doppler ankle artery pressure was similar among diabetic and non-diabetic patients and was also similar in patients with rest pain alone and those with both rest pain and ischaemic tissue necrosis.

International Vascular Symposium working party definition

Some 109 patients (51 per cent) fulfilled the definition proposed by the IVS working party; 78 (72 per cent) had rest pain with a systolic ankle artery pressure <40 mmHg, 67 (61 per cent) rest pain with ischaemic tissue necrosis plus systolic ankle pressure <60 mmHg, and 36 (33 per cent) had all three.

Modified International Vascular Symposium working party definition

A total of 153 patients (72 per cent) fulfilled the simplification of the IVS working party definition; 83 (54 per cent) had rest pain and a systolic ankle pressure <40 mmHg, 111 (73 per cent) rest pain and ischaemic tissue necrosis, and 41 (27 per cent) had all three.

European Working Group definition

Some 104 patients (49 per cent) fulfilled the definition suggested by the European Working Group on Critical Limb Ischaemia (rest pain and/or ischaemic tissue necrosis plus an ankle pressure <50 mmHg; 53 (51 per cent) had ischaemic tissue necrosis.

The statistical power of these definitions is summarized in *Tables 2–5*. Both the original and modified IVS criteria, but not the European definition, had significant statistical power in the prediction of amputation for the study group as a whole (*Table 2*). However, when considering only patients in whom revascularization failed or was not attempted, all three were able to predict amputation in a proportion of patients (*Table 2*). The simplified definition was most sensitive. The predictive value of fulfilling each definition is broadly similar, ranging from 70 to 75 per cent.

No definition was able to predict those patients in whom grafts were likely to occlude (*Table 3*).

Table 2 *Prediction of amputation, observed in 76 of 213 patients*

	No.	P*	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Data from whole study group (n = 213)					
IVS working party	109	<0·04	61	54	42
Modified IVS working party	153	<0·003	84	35	42
European Working Group	104	n.s.	55	55	40
Data from patients in whom reconstruction was not undertaken or failed (n = 120)					
IVS working party	62	<0·01	61	64	74
Modified IVS working party	92	<0·01	84	36	70
European Working Group	56	<0·01	55	68	75

IVS, International Vascular Symposium. *χ^2 test; n.s., not significant

Table 3 *Prediction of graft occlusion, observed in 54 of 147 reconstructions*

	No.	P*	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
IVS working party	74	n.s.	53	50	37
Modified IVS working party	96	n.s.	69	34	38
European Working Group	73	n.s.	51	48	34

IVS, International Vascular Symposium. *χ^2 test; n.s., not significant

Table 4 *Prediction of mortality, observed in 72 of 213 patients*

	No.	P*	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Data from whole study group ($n = 213$)					
IVS working party	109	n.s.	51	49	34
Modified IVS working party	153	<0·04	81	33	38
European Working Group	104	n.s.	50	52	35
Data from patients in whom reconstruction was not undertaken or failed ($n = 120$)					
IVS working party	62	n.s.	52	49	44
Modified IVS working party	92	n.s.	85	29	48
European Working Group	56	n.s.	46	53	43
Data from patients in whom reconstruction was not attempted ($n = 69$)					
IVS working party	35	n.s.	56	55	57
Modified IVS working party	57	<0·007	92	30	59
European Working Group	31	n.s.	50	61	58

IVS, International Vascular Symposium. *χ^2 test; n.s., not significant

Table 5 *Prediction of amputation in relation to diabetes*

	No.	P*	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
IVS working party					
All	109	<0·04	61	54	42
Non-diabetic	90	<0·01	65	56	41
Diabetic	19	n.s.	47	38	47
Modified IVS working party					
All	153	<0·003	84	35	42
Non-diabetic	120	<0·01	81	39	38
Diabetic	33	n.s.	95	6	55
European Working Group					
All	104	n.s.	55	55	40
Non-diabetic	87	n.s.	58	55	38
Diabetic	17	n.s.	47	50	53

IVS, International Vascular Symposium. *χ^2 or Fisher's exact test; n.s., not significant

Only the modified definition was able to predict the likelihood of death when considering the study population as a whole (*Table 4*). Surprisingly, no definition was able to predict death in patients whose grafts occluded or in whom no attempt at revascularization was made. When considering only those patients in whom reconstructive procedures were not undertaken, only the modified definition was able to predict the likelihood of death, albeit with poor specificity and positive predictive value (*Table 4*).

Table 5 shows the effect of the ability to predict amputation produced by excluding diabetic patients; there is some statistical improvement. This improvement is associated with slightly better (but still poor) sensitivity, specificity and positive predictive value. By contrast, no definition was able to predict outcome in a subgroup comprised wholly of diabetics.

Discussion

These data support the findings of previous studies, that primary amputation carries a higher mortality rate than arterial reconstruction. This may be a self-fulfilling prophecy, because high-risk patients are probably more likely to be offered amputation (as a rapid surgical solution) than those at low risk. Nevertheless, it suggests that mortality is related to the severity of disease. Furthermore, the acceptable operative mortality rate for reconstruction should encourage surgeons to pursue revascularization.

It is surprising that, although all of the definitions examined were able to predict amputation in patients whose critical ischaemia was not corrected by direct arterial reconstruction, only the modified definition had any statistical power in predicting mortality. It had been expected that patients with more severe clinical presentations might harbour more severe coronary and cerebrovascular disease and, therefore, be at greater risk of a fatal cardiovascular event. It is common experience that there is poor correlation between the site and extent of arterial occlusion and the severity of clinical presentation.

That diabetic and non-diabetic patients had similar ankle artery pressures is surprising. Diabetics are, nevertheless, more likely to come to amputation than non-diabetic patients. The similarity in pressures between these groups appears at odds with accepted wisdom, which is that diabetics are more likely to have spuriously high ankle artery pressures. The greater amputation rate among diabetic patients probably testifies to a more aggressive small vessel disease and a greater susceptibility to infection. The inability of any definition to predict outcome for the diabetic subgroup lends weight to the IVS working party's initial suggestion that 'diabetics should be excluded from the ideal clinical study'. It seems that this disease adds a significant and unpredictable element to the clinical outcome and the present authors also feel that this subgroup should be analysed separately.

The present data do not support the hypothesis[4] that reconstruction undertaken for critical ischaemia (by any of the current definitions) carries a greater risk of graft occlusion than that performed for rest pain alone. This may be a consequence of inadequacies in the definitions themselves but, in view of the fact that they are all able to predict amputation, it is probably a significant finding. Perhaps surgical skill (particularly in more distal operations) and the site of arterial occlusion are such major factors in determining outcome that they obscure the prognostic value of clinical presentation. The former is not surprising and has also been suggested in carotid endarterectomy[5].

This study includes patients from nine centres. Although all contributing surgeons share a special interest in vascular surgery, the investigative, operative and follow-up facilities vary widely between centres. These variables, together with the small numbers of operations within each level of surgical difficulty (suprainguinal, femoropopliteal, femorodistal, various angioplasties) conspire to prevent meaningful comparison between centres.

It is not possible to study the natural history of very severe lower-limb ischaemia. It is therefore necessary to infer outcome from patients in whom direct arterial reconstruction is not undertaken, or from those in whom it fails. It is clear from the present data that such patients have a significantly worse outlook than those who undergo successful revascularization. However, it must be remembered that they may represent a self-selected subgroup with a disproportionately poor prognosis.

All three definitions were able to predict a significant number of the patients who ultimately came to amputation, but not of those who died. The differences between the definitions lie in their sensitivities, specificities and predictive values. None was satisfactory, and it is not surprising (given that each is composed of the same essential ingredients in slightly differing proportions) that what one lacked in specificity another lacked in sensitivity. These results may have been less disappointing if the definitions had been applied to a group less preselected for severe ischaemia, but it seemed appropriate to use a history of rest pain as the 'screening test' and one of the definitions as the 'definitive test'.

All the proposed definitions of critical ischaemia seem inadequate. The reason for this is not immediately apparent, but the distribution of ankle artery pressures may offer a clue: the distribution of pressures is not normal. It is conceivable that an excessive number of patients were recorded as having a pressure of 0 mmHg because of difficulty in measuring very low pressure. If this is the case, then these data cannot be considered to have either corroborated or refuted any of the definitions, but they have revealed a significant practical problem in their application. In any event, the addition of further defining criteria, independent of observer error, would be beneficial. Herein lies the difficulty. Cardiac surgeons can obtain prognostic information about the myocardium from the electrocardiogram and the anatomical distribution of disease, but no similar techniques are available to the peripheral vascular surgeon. Toe artery pressure measurements have been suggested as a more accurate assessment[6,7], but the measurement is more difficult and prone to variability[8]. Dowd *et al.*[9] improved the specificity of definition by adding transcutaneous oxygen measurement, but this is a time-consuming test that is not available to all vascular surgeons. Furthermore, there is considerable overlap in the values obtained for patients without ischaemic rest pain and those with rest pain and ischaemic ulceration[10]. Another interesting, but currently experimental, technique for identifying ischaemic tissue is phosphorus-31 magnetic resonance spectroscopy[11].

It is suggested that the various national vascular societies and journals are now in a position to agree a unified definition of critical ischaemia. The European definition has performed disappointingly and the modified IVS definition has a slight advantage, probably because it was based on prospective data. Despite a similarity in ankle artery pressures between diabetic and non-diabetic patients, the inability of any of these definitions to predict outcome among diabetics suggests that these patients should be excluded or analysed separately. Investigators might also try to identify simple widely applicable laboratory investigations that will improve predictive value.

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References

1. Bell PRF, Charlesworth D, DePalma RG *et al.* The definition of critical ischaemia of a limb. *Br J Surg* 1982; **69**: S2.
2. Wolfe JHN. The definition of critical ischaemia – is this a concept of value? In: Greenhalgh RM, Jamieson CW, Nicolaides AN, eds. *Limb Salvage and Amputation for Vascular Disease*. London: WB Saunders, 1988: 3–10.
3. European consensus on critical limb ischaemia. *Lancet* 1989; **i**: 737–8.
4. Thompson JE. Why do reported graft patency rates vary so widely? In: Greenhalgh RM, ed. *Femoro-distal Bypass*. London: Pitman, 1981: 45–50.
5. Browse NL, Ross-Russell R. Carotid endarterectomy and the Javid shunt: the early results of 215 consecutive operations for transient ischaemic attacks. *Br J Surg* 1984; **71**: 53–7.
6. Ramsey DE, Manke DA, Sumner DS. Toe blood pressure. A valuable adjunct to ankle pressure measurement for assessing peripheral arterial disease. *J Cardiovasc Surg (Torino)* 1983; **24**: 43–8.
7. Carter SA, Lezack JD. Digital systolic pressures in the lower limb in arterial disease. *Circulation* 1971; **43**: 905–14.
8. Sondgeroth TR, Salles-Cunha SX, Vollrath KD, Towne JB. Variability of toe pressure measurements. *Bruit* 1989; **6**: 14–16.
9. Dowd GSE, Linge K, Bentley G. Measurement of transcutaneous oxygen pressure in normal and ischaemic skin. *J Bone Joint Surg [Br]* 1983; **65-B**: 79–83.
10. Larsen JF, Jensen BV, Christensen KS, Egeblad K. Forefoot transcutaneous oxygen tension at different leg positions in patients with peripheral vascular disease. *Eur J Vasc Surg* 1990; 4: 185–9.
11. Hands LJ, Sharif MH, Payne GS, Morris PJ, Radda GK. Muscle ischaemia in peripheral vascular disease studied by ^{31}P-magnetic resonance spectroscopy. *Eur J Vasc Surg* 1990; 4: 637–42.

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Intermittent claudication incites systemic neutrophil activation and increased vascular permeability

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Reperfusion following severe ischaemia incites a systemic response involving neutrophil activation and vascular injury. Recent work suggests that intermittent claudication may also be capable of inducing similar changes, reversible by revascularization. This observation may have implications for the treatment of claudication and explain the high associated cardiovascular mortality. This hypothesis was investigated using an in vivo *model. Rats underwent repeated hindlimb stimulation after common iliac artery ligation. Intravital fluorescence microscopy was used to observe postcapillary venules of the tibialis anterior muscle in the hindlimb. This revealed a bilateral increase in leucocyte–endothelial adhesion and vascular permeability to albumin after unilateral subtotal ischaemia and muscle stimulation, associated with increased urinary albumin excretion. These results provide further evidence supporting the association of intermittent claudication with potentially deleterious systemic manifestations.*

Reperfusion following severe ischaemia initiates a systemic response. Inflammatory mediators stimulate neutrophils to release proteolytic enzymes and oxygen-derived free radicals. The latter cause systemic vascular injury by peroxidation of endothelial cell membrane lipids, resulting in increased vascular permeability[1,2]. Reduced neutrophil filterability, increased serum lysozyme activity, raised lipid peroxidation and increased urinary albumin excretion have been observed in claudicants after exercise, suggesting that transient local ischaemia is associated with neutrophil activation, oxygen-derived free radical activity and increased vascular permeability[3,4].

The hypothesis that the mild transient muscle ischaemia of claudication is capable of inducing systemic vascular injury is supported by evidence from an *in vivo* model of claudication[5] in which electron microscopy demonstrated evidence of systemic vascular injury (endothelial cell swelling) after stimulation of ischaemic hindlimb muscles[6].

Intravital fluorescence microscopy may be used to study leucocyte behaviour[7] and vascular permeability to macromolecules[8] in the microcirculation. The present study used this technique to investigate whether hindlimb claudication in an animal model produced systemic changes in white cell adhesion and vascular permeability. Certain changes might support the previous findings in human claudicants, particularly if associated with increased urinary albumin excretion.

Materials and methods

The model has been described previously[6]. Briefly, male Sprague–Dawley rats underwent laparotomy, ligation of the right common iliac artery and implantation of a pair of electrodes adjacent to the lateral popliteal nerve in the right hindlimb. The hindlimb muscles were then subjected to electrical stimulation (0·3-ms impulses, 10 Hz) at a voltage sufficient to induce palpable muscle twitching without apparent discomfort (1·5–2·3 V) for 10–15 min seven times daily for 14 days (ligated–stimulated group). This regimen resulted in circulatory and morphological changes similar to those seen in human claudicants, without muscle necrosis[5,6].

Alternatively, rats underwent artery ligation and sham stimulation (ligation only group), muscle stimulation after sham laparotomy (stimulation only group) or both sham laparotomy and sham stimulation (control group). In addition, another group underwent left common iliac artery ligation and stimulation of the left hindlimb muscles (contralateral group).

Leucocyte behaviour

Acridine orange, a fluorescent dye for labelling white blood cells[9], was used to study leucocyte behaviour in the tibialis anterior muscle of the right hindlimb by intravital fluorescence microscopy.

Rats were anaesthetized by intraperitoneal injection of pentobarbitone sodium (5 mg per 100 g body-weight) and a jugular vein was cannulated to allow subsequent administration intravenously. The animals were placed supine on a specially designed stage with the right hindlimb held firmly in extension and the skin and fascia carefully stripped from the anterior surface of the tibialis anterior. The muscle microcirculation was then examined with a modified Zeiss ACM microscope (Zeiss, Oberkochen, Germany) equipped with a mercury incident light source and a water-immersion ×25 objective lens, allowing direct observation or videoscreen viewing via a camera. Information was stored on videocassette for subsequent analysis on slow-motion playback. Microcirculatory observation concentrated on postcapillary venules, the expected site of maximal neutrophil-mediated vascular injury[10]. Throughout the procedure the muscle surface was superfused with a buffered isotonic solution of 1 per cent gelatin in physiological saline (37°C, pH 7·4, equilibrated with 95 per cent nitrogen–5 per cent carbon dioxide).

Four rats from each of the five groups were examined. Acridine orange (0·1 per cent in saline) was infused via the jugular cannula at 0·2 ml/min after an initial bolus injection of 0·5 ml, and mild (1 Hz) hindlimb stimulation was commenced. After 10 min of stimulation, postcapillary venules were observed for periods of 1 min; five were examined from each rat during a 10-min period, so 20 venules from each group were studied. On later video analysis, the total number of leucocytes passing through the venules was recorded and the percentage adhering to the endothelium determined. Leucocytes observed to be completely stationary for at least 5 s were classed as adherent, not those seen rolling slowly along a venule.

Mean percentage adherence was calculated for the five groups. The data were distributed normally and differences between groups determined by Student's unpaired t test and confirmed by analysis of variance (ANOVA).

Vascular permeability

A further 20 rats (four from each group) were prepared as above for intravital observation of the right tibialis anterior muscle. Fluorescein isothiocyanate-labelled bovine serum albumin (FITC–BSA) (8·25 per cent in water) was injected via the jugular cannula at 1 ml per 100 g body-weight, mild hindlimb stimulation was commenced and the microcirculation scanned for 30 min. No single area was observed for >60 s at a time to avoid potential vascular injury from prolonged excitation of the FITC[11]. All rats were killed by an overdose of

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anaesthetic 1 h after FITC–BSA injection and the bladder completely drained of urine by laparotomy and direct puncture.

FITC–BSA in 50 per cent sucrose solution was applied to a 20-cm Sephacryl (Pharmacia; Milton Keynes, UK) column and the fraction corresponding to the molecular weight of BSA (69 kDa) identified. The fluorescence of this fraction was compared with that of the original solution by fluorescence spectrophotometry (LS-2 Fluorometer; Perkin–Elmer, Beaconsfield, UK), which demonstrated that >90 per cent of the FITC was bound to albumin. Urine samples in sucrose were then applied to the column, the albumin fraction collected and the fluorescence of each sample determined in arbitrary fluorescence units. Urinary creatinine was determined and a BSA:creatinine ratio (expressed in fluorescence units/millimole) calculated to compensate for any differences in urinary flow rate between the rats.

Leakage of FITC–BSA from postcapillary venules was estimated by assessment of the video pictures and differences between the BSA:creatinine ratios of the groups analysed by the Wilcoxon rank sum test.

Results

Figure 1 shows a videoscreen view of leucocytes passing through a postcapillary venule of a ligated–stimulated rat. There was no significant difference between groups in the total number of white blood cells passing through the venules in 1 min, but the lowest mean leucocyte flux (41·5 (range 21–52) cells/min) was in the control group and the highest (46·4 (range 32–59) cells/min) in the ligated–stimulated rats. The percentage of adherent white cells did not increase significantly after muscle stimulation alone but was significantly higher in the ligation only group compared with controls ($P < 0{\cdot}01$) (*Figure 2*). Leucocyte adherence was greatly increased in ligated–stimulated rats ($P < 0{\cdot}001$) and significantly higher than after either stimulation only or ligation alone. Adherence was also significantly increased in the right tibialis anterior muscle after contralateral (left-sided) 'claudication' ($P < 0{\cdot}01$). ANOVA confirmed significant differences between the group means ($P < 0{\cdot}001$).

There was little discernible leakage of fluorescent albumin through the postcapillary venules of control rats: the vessel image remained clear throughout the 30-min observation period (*Figure 3*). Similar pictures were obtained in stimulation only animals but in the ligated–stimulated group there was gradual blurring of the vessel margins over the 30 min, indicating leakage of FITC–BSA (*Figure 4*). This was also seen, to a lesser extent, in the ligation only and contralateral ligated–stimulated rats.

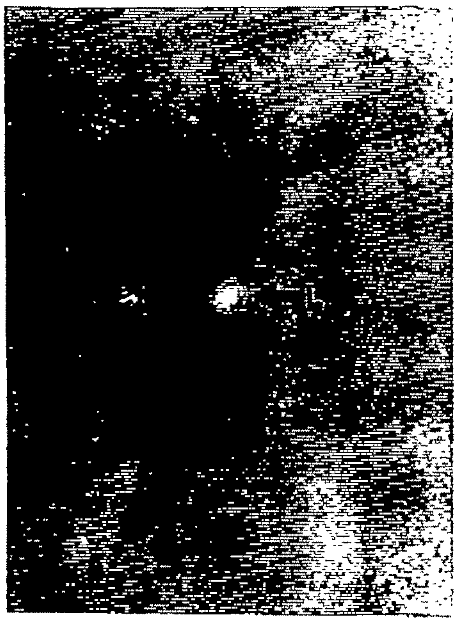

Figure 1 *Videoscreen view of acridine orange-labelled leucocytes passing through a postcapillary venule in the tibialis anterior of a ligated–stimulated rat. L, leucocyte that has become adherent to the endothelium*

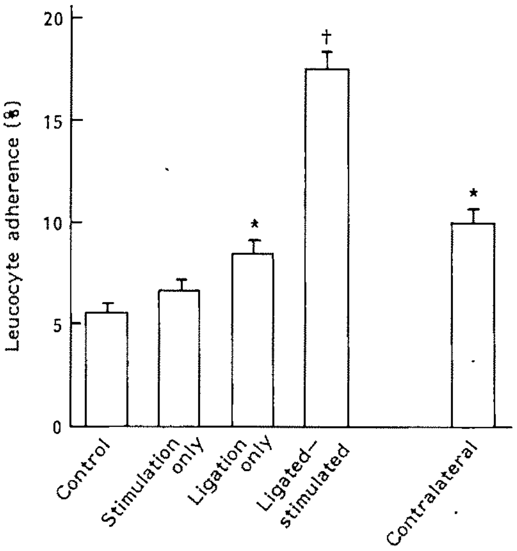

Figure 2 *Mean(s.e.m.) percentage of adherent leucocytes in postcapillary venules of the tibialis anterior muscle of the right hindlimb in rats.* *$P < 0{\cdot}01$; †$P < 0{\cdot}001$ (versus *control, Student's unpaired* t *test*)

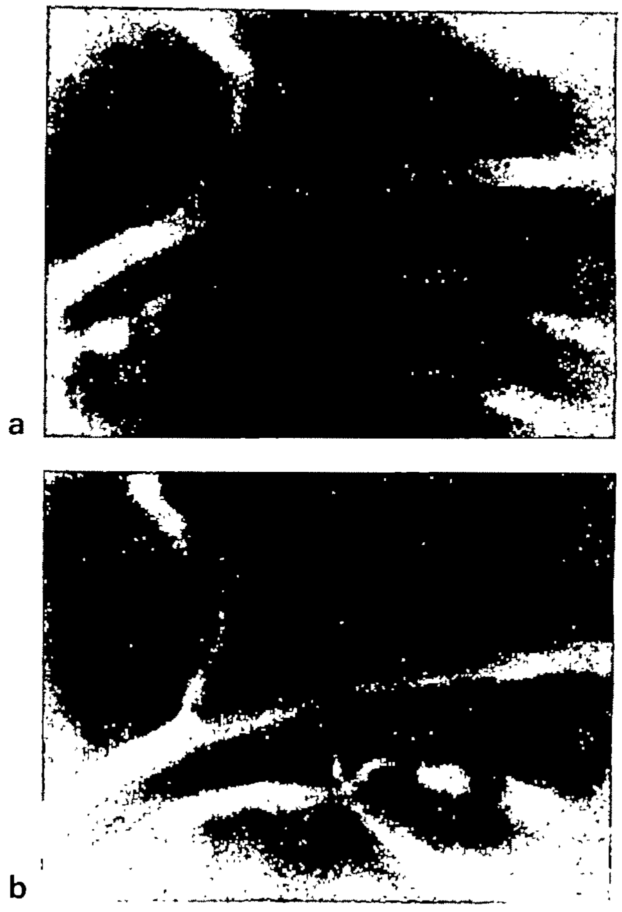

Figure 3 *Right tibialis anterior postcapillary venule in a control rat* **a** *immediately and* **b** *30 min after injection of fluorescein isothiocyanate-labelled bovine serum albumin*

Similarly, the BSA:creatinine ratio showed no increase after stimulation only but rose significantly after common iliac artery ligation ($P < 0{\cdot}05$) (*Figure 5*). There was a significant increase ($P < 0{\cdot}01$) in the 'claudicant' rats (ligated–stimulated and contralateral). Again, this was significantly higher than after

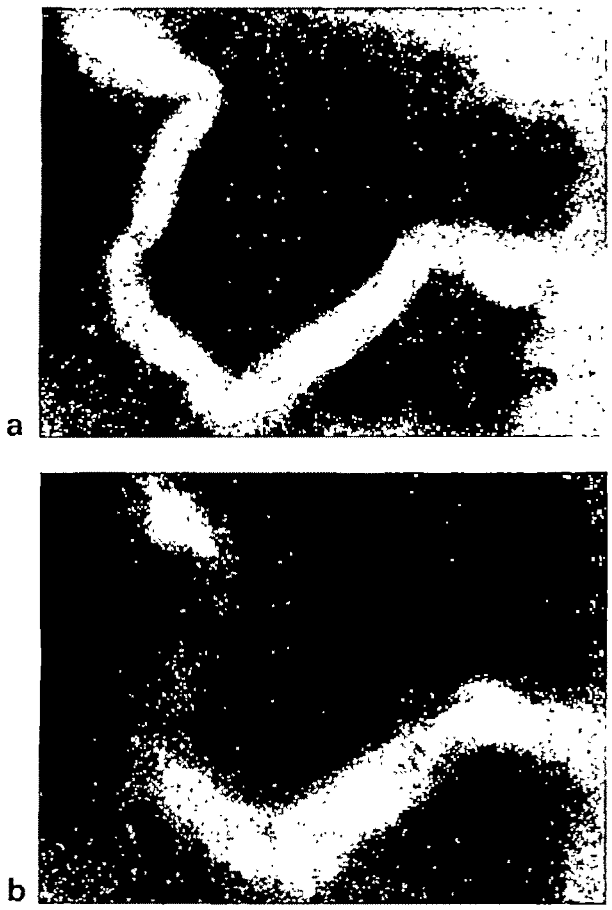

Figure 4 *Right tibialis anterior postcapillary venule in a ligated–stimulated rat* **a** *immediately and* **b** *30 min after injection of fluorescein isothiocyanate-labelled bovine serum albumin*

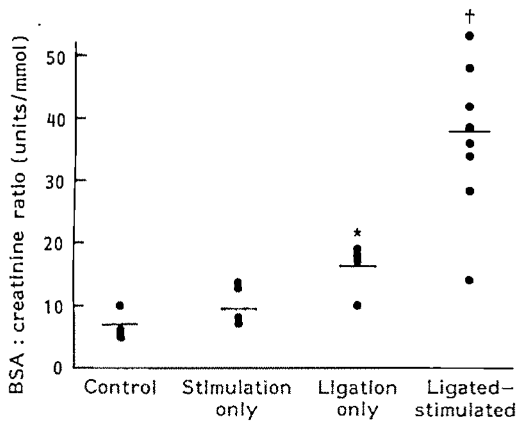

Figure 5 *Urinary bovine serum albumin (BSA):creatinine ratio 1 h after fluorescein isothiocyanate-labelled BSA injection. Bars are means. The ligated–stimulated group in this instance includes ligated–stimulated and contralateral ligated–stimulated rats.* $^{*}P < 0{\cdot}05$; $^{\dagger}P < 0{\cdot}01$ (versus *controls, Student's unpaired* t *test)*

ligation or stimulation alone. Ligated–stimulated and contralateral rats were analysed together because both groups had undergone unilateral artery ligation and stimulation; it was felt that for the purpose of studying the BSA:creatinine ratio they were essentially identical. The ratio was, indeed, similar between the two groups.

Discussion

The present study has demonstrated increased leucocyte adhesion in the muscle microcirculation of both the claudicating and contralateral limbs and a systemic increase in vascular permeability associated with raised urinary albumin excretion. Neutrophil–endothelial cell adhesion has a central role in reperfusion injury[11] and increased white cell adhesion has previously been demonstrated after ischaemia by intravital microscopy[12,13]. This technique cannot differentiate between neutrophils and monocytes, but the rapid response to the ischaemic stimulus suggests involvement of the former.

The present study has relied on measuring changes in urinary albumin excretion to quantify indirectly changes in vascular permeability seen on microscopy. Although this endorses the previous findings in human claudicants that urinary albumin excretion is proportional to the severity of ischaemia[14], a direct measurement is desirable, particularly to investigate therapeutic modification of the changes observed. In the hamster cheek pouch model quantification is relatively simple because leakage occurs at discrete sites[15]. This is not the case in skeletal muscle, but a promising technique for use in this model involves a computer program that quantifies fluorescence along a raster line of a videoscreen[16]. The suitability of this method for use in the present preparation is being investigated.

Peripheral vascular disease is a marker of generalized atherosclerosis and claudicants, particularly those with severe disease, suffer from a high mortality rate[17]. Active treatment aimed at modifying the progression and complications of atherosclerosis may be of benefit to patients with intermittent claudication[18]. Neutrophil activation and adhesion, lipid peroxidation and increased vascular permeability have been implicated in atherogenesis[19,20]. The possibility that these events are precipitated by localized muscle ischaemia reinforces the importance of holistic management strategies and suggests that reversing the systemic response to claudication is desirable. In conclusion, the present results provide further evidence to suggest that intermittent claudication incites a systemic response that may represent a systemic reperfusion injury involving neutrophil activation and vascular damage.

References

1. Welbourn CRB, Goldman G, Paterson IS, Valeri CR, Shepro D, Hechtman HB. Pathophysiology of ischaemia reperfusion injury: central role of the neutrophil. *Br J Surg* 1991; **78**: 651–5.
2. Anner H, Kaufman RP, Valeri CR, Shepro D, Hechtman HB. Reperfusion of ischemic lower limbs increases pulmonary microvascular permeability. *J Trauma* 1988; **28**: 607–10.
3. Hickey NC, Gosling P, Baar S, Shearman CP, Simms MH. Effect of surgery on the systemic inflammatory response to intermittent claudication. *Br J Surg* 1990; **77**: 1121–4.
4. Shearman CP, Gosling P, Gwynn BR, Simms MH. Systemic effects associated with intermittent claudication: a model to study biochemical aspects of vascular disease. *Eur J Vasc Surg* 1988; **2**: 401–4.
5. Hudlicka O, Eggington S, Brown MD, Dawson JM. Blood flow, performance and capillary ultrastructure in ischaemic rat fast muscles: effect of chronic electrical stimulation. *J Physiol (Lond)* 1991; **435**: 15P.
6. Hickey NC, Hudlicka O, Simms MH. Claudication induces systemic capillary endothelial cell swelling. *Eur J Vasc Surg* 1992; **6**: 36–40.
7. Blixt A, Braide M, Myrhage R, Bagge U. Vital microscopic studies on the capillary distribution of leukocytes in the rat cremaster muscle. *Int J Microcirc Clin Exp* 1987; **6**: 273–86.
8. Suval WD, Duran WN, Boric MP, Hobson RW, Berendsen BP, Ritter AB Microvascular transport and endothelial cell alterations preceding skeletal muscle damage in ischemia and reperfusion injury. *Am J Surg* 1987; **154**: 211–18.
9. Dawson JM, Hudlicka O. The effects of long term administration of prazosin on the microcirculation in skeletal muscles. *Cardiovasc Res* 1989; **23**: 913–20.
10. Williams TJ, Jose PJ, Forrest MJ, Wedmore CV, Clough GF. Interactions between neutrophils and microvascular endothelial cells leading to cell emigration and plasma protein leakage. In: Meiselman HJ, Lichtman MA, Lacelle PL, eds. *White Cell Mechanics. Basic Science and Clinical Aspects.* New York: Alan R Liss, 1984: 195–208.
11. Reed MWR, Miller FN. Importance of light dose in fluorescent

microscopy. *Microvasc Res* 1988; **36**: 104–7.
12. Schmid-Shonbein GW. Granulocyte activation and capillary obstruction. *Monogr Atheroscler* 1990; **15**: 150–9.
13. Zeintl H, Sack FU, Intaglietta M, Messmer K. Computer assisted leukocyte adhesion measurement in intravital microscopy. *Int J Microcirc Clin Exp* 1989; **8**: 293–302.
14. Hickey NC, Shearman CP, Gosling P, Simms MH. Assessment of intermittent claudication by quantitation of exercise-induced microalbuminuria. *Eur J Vasc Surg* 1990; **4**: 603–6.
15. Persson NH, Erlansson M, Svensjo E, Takolander R, Bergqvist D. The hamster cheek pouch – an experimental model to study postischemic macromolecular permeability. *Int J Microcirc Clin Exp* 1985; **4**: 257–63.
16. Miller FN, Joshua IG, Anderson GL. Quantitation of vasodilator-induced macromolecular leakage by *in-vivo* fluorescent microscopy. *Microvasc Res* 1982; **24**: 56–67.
17. O'Riordan D, Horgan A, Fitzgerald L, O'Donnell J. Realistic expectations for the patient with intermittent claudication. *Br J Surg* 1990; **77**: 349 (Abstract).
18. Prevention of Atherosclerotic Complications with Ketanserin (PACK) Trial Group. Prevention of atherosclerotic complications: controlled trial of ketanserin. *BMJ* 1989; **298**: 424–30.
19. Kling D, Holzschuh T, Strohschneider T, Betz E. Enhanced endothelial permeability and invasion of leukocytes into the artery wall as initial events in experimental arteriosclerosis. *Int Angiol* 1987; **6**: 21–8.
20. Stringer MD, Gorog PG, Freeman A, Kakkar VV. Lipid peroxides and atherosclerosis. *BMJ* 1989; **298**: 281–4.

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The future of vascular surgery

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Peripheral vascular disease is a growing problem in the developed world because of smoking and an increasingly elderly population. The rise in workload detailed by the Vascular Registry in Southern Sweden[1] shows that the number of operations per 10^6 inhabitants per year increased from fewer than 300 in 1980 to more than 1500 in 1987. Although there are no accurate data for the UK, there is every reason to suppose that a similar increase has occurred. In response to this workload, the Vascular Advisory Committee of The Royal College of Surgeons of England has suggested that there should be two vascular surgeons per 500 000 people[2]. Unfortunately, despite a recent increase in consultant appointments, these recommendations have yet to be realized; neither do they take into account the increasing work performed by vascular radiologists in conjunction with surgeons.

The Vascular Surgical Society of Great Britain and Ireland was founded 25 years ago and with 450 members now represents most of the vascular surgeons in these countries. At its inception surgery was the only realistic treatment available for peripheral vascular disease and, not surprisingly, surgeons felt that they 'owned' the specialty. However, although there have been considerable advances in what the scalpel can achieve, there has been a recent shift towards improved diagnostic methods and less invasive forms of treatment such as percutaneous transluminal angioplasty and thrombolysis. These improvements have come about largely through a good working relationship between vascular radiologists, who have developed the techniques, and vascular surgeons, who maintain overall responsibility for patients. This change in emphasis was well illustrated at the 26th meeting of the Vascular Surgical Society in London in November 1992. Of the 66 papers presented, only 25 were truly surgical, with 18 concentrating on investigative techniques and angioplasty, and a further 12 on pharmacological treatments including thrombolysis[3]. The majority had a 'non-surgical' author. Despite both this and the advances made in vascular treatment by radiologists and physicians, the Vascular Surgical Society has only four associate (non-voting) members. Indeed, the Society's constitution states that ordinary (voting) members should normally be consultant surgeons with a direct interest in vascular surgery. The potential limitations of this restrictive policy are obvious.

In response to the shift toward less invasive endovascular procedures, the Society recently accepted the following recommendations from its working party:

1. That the Society encourages the involvement of vascular surgeons in endovascular procedures as a complementary activity to the interventions of vascular radiologists.
2. That the Society advises the Surgical Advisory Committee in general surgery that experience in endovascular techniques is introduced into approved vascular surgical training programmes.

These recommendations were made with little dialogue between the surgeons and other interested groups, such as the British Society of Interventional Radiologists. In most successful vascular treatment centres a necessarily close working relationship exists between vascular surgeons and vascular radiologists and, not surprisingly, these recommendations have caused considerable disquiet. An interventional radiologist does not need to know how to perform a femoropopliteal graft but rather needs to understand the indications and limitations of the technique; similarly a vascular surgeon need not attempt to replace a vascular radiologist but rather to understand their work. Considerable progress, made already through this healthy close working relationship, should not be jeopardized by a unilateral policy introduced without the involvement of the whole vascular service. Just as it should not be the intention of the vascular surgeon to usurp the radiologist, the latter should have a similar regard for the surgeon and not work independently of him or her, but rather as a partner. An understanding by all parties of the various therapeutic methods can serve only to benefit the patient and improve the quality of service that is provided. It is reassuring that constructive discussions have now been held between the Vascular Surgical Society, the British Society of Interventional Radiologists and the Royal Colleges of Surgeons and Radiologists. Recommendations on training in endovascular procedures have now been formulated and should be published soon.

The vast majority of endovascular procedures are performed by interventional radiologists and rightly so, for it is they who are trained in radiation physics, equipment assessment and associated aspects of safety. Subsequent training in endovascular techniques, as with surgery, is a gradual learning process taking many years. Vascular surgeons are unlikely to gain sufficient experience of these techniques to advance past the 'learning curve', either as trainees or consultants. However, there may be a need for adjuvant angioplasty during surgery and it may well be appropriate for this to be carried out by a suitably trained vascular surgeon. It may be performed better as a joint or staged procedure by the radiologist, but the surgeon should not be prevented from doing it if competent. The lack of an interventional radiologist is not a good reason for surgeons to perform angioplasty. Certainly the concept of a vascular surgeon exposing arteries to perform a procedure that could be carried out percutaneously is to be condemned. Similarly, direct access to the interventional radiologist by the general practitioner is to be discouraged as this risks treatment of the vascular lesion rather than of the whole patient. In the USA this has led to an increase in the number of unnecessary angioplasties[4].

The Vascular Surgical Society must take the lead on these issues and not fight a rearguard action to protect its own interests. Good working practice should stem from what is practical and best for patients. The Society can look to its own to improve the quality of vascular surgical training. Where there are inadequacies in the number or quality of trained vascular radiologists, this should be addressed by the Vascular Surgical Society (or its appropriately named successor), by the Royal College of Radiologists and by the British Society of Interventional Radiologists. Only in this way can we hope to improve the quality of the service and stop the potentially harmful dissipation of talent into isolated groups. For instance, a European working group on medical angiology has already been formed and has drawn up a document entitled 'The case for the specialty of medical angiology'[5]. Similar suggestions have been made in the USA[6]. Presumably these medical angiologists envisage a similar role to that of their cardiological colleagues, with overall responsibility for patients with vascular disease, involvement in diagnostic and percutaneous techniques, and ultimate relegation of vascular surgeons and radiologists to the role of technicians.

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One simple step would be for the Vascular Surgical Society of Great Britain and Ireland to drop the isolationist word 'surgical' from its name and welcome other interested groups into the Society as full members. The Society cannot prevent other clinicians from practising 'vascular medicine' if they so wish, and the key to future cooperation is improved communication. Similarly, more varied training schemes would allow trainees with an interest in vascular disease to be exposed to the many facets of the vascular service and to the concept of the team approach. These would be the first steps toward creating a truly integrated vascular service. Although, in the long term, a unified vascular training scheme that includes medicine, surgery and radiology might appear attractive, it is difficult to envisage how this could develop as this concept cuts across traditional preserves of the interested parties, especially those of the Royal Colleges.

References

1. Vascular Registry in Southern Sweden (VRISS). The vascular registry – a responsibility for all vascular surgeons. *Eur J Vasc Surg* 1987; 1: 219–27.
2. Darke SG. The provision of vascular services. *Eur J Vasc Surg* 1987; **1**: 217–19.
3. Abstracts from the 26th Annual General Meeting of the Vascular Society of Great Britain and Ireland. *Br J Surg* 1993 (in press).
4. Tunis RT, Bass EB, Steinberg EP. The use of angioplasty, bypass surgery, and amputation in the management of peripheral vascular disease. *N Engl J Med* 1991; **325**: 556–62.
5. Bartolo M, Boccalon H, Bollinger A *et al.* The case for the specialty of medical angiology. *Vasa* 1992; 1: 3–5.
6. Cooke JP, Dzau VJ. The time has come for vascular medicine. *Ann Intern Med* 1990; **112**: 138–9.

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Short note

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Access to convalescent beds in vascular surgery

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The past decade has seen considerable advances in anaesthetic and vascular surgical practice, and a greater number of elderly patients undergo major reconstructive and limb salvage procedures than ever before. One disadvantage of this trend is that an increasing number of patients occupy acute surgical beds for convalescent purposes, and this may compromise a unit's capacity to meet ongoing vascular and general surgical commitments. Moreover, it is often perceived that the problem is aggravated by the loss of convalescent beds throughout the health service.

Methods

A postal survey of 333 consultant members of the Vascular Surgical Society of Great Britain and Ireland was conducted to assess trends in the availability of convalescent facilities for vascular patients.

Results

Of 236 respondents, only 52 (22 per cent) had access to convalescent beds; there was no difference in availability between consultants working in teaching (18 of 80) or district general (34 of 156) hospitals. Both groups with access had a median of 10 beds at their disposal. Compared with 10 years ago, 144 consultants (61 per cent) noted no change in convalescent facilities, while three (1 per cent) had more beds. Access to convalescent beds had, however, decreased for 89 consultants (38 per cent), 70 (79 per cent) reporting a complete loss of beds.

On the day of completing the survey, a median of 3 vascular patients could have been transferred from each consultant's acute surgical ward to convalesce if beds had been available. This was higher for teaching (median 5 (95 per cent confidence interval (c.i.) 4–6)) than district general (median 3 (95 per cent c.i. 2–4)) hospitals ($P < 0{\cdot}0001$, Mann–Whitney U test). However, where consultants had access to convalescent beds, the median (95 per cent c.i.) number of patients who could be transferred was less (1 (0–2)) than for those with no access (3 (2–4)) ($P < 0{\cdot}0001$, Mann–Whitney U test).

Overall, 106 surgeons (45 per cent) cancelled vascular cases more than once a fortnight, 13 (6 per cent) cancelled none and the remainder cancelled fewer than one a month. Teaching hospital consultants were more likely to cancel cases more than once a fortnight than their district general hospital counterparts (odds ratio 3·5 (95 per cent c.i. 2·0–6·2)), as were consultants with no access to convalescent beds (odds ratio 6·5 (95 per cent c.i. 2·8–14·0)).

Discussion

With the trend towards complicated limb-salvage procedures and operations on an increasingly elderly population, it is inevitable that some patients may require a longer period of convalescence and rehabilitation than usual. Few, however, require intensive medical or nursing care after the early postoperative period.

Although this study represents only 236 respondents, it suggests that the minority of vascular surgeons have access to convalescent beds and few have separate rehabilitation units for amputees. As expected, consultants with no convalescent facilities had a greater number of patients occupying acute surgical beds and this has implications for cost-effective utilization of limited resources. In addition, while there are many reasons for case cancellation (seasonal variations, bed availability, intensive therapy unit facilities, staffing, etc.), surgeons with no access to convalescent beds were more likely to cancel cases on a regular basis, although an unknown proportion of these may be varicose vein operations. While these problems may be eased with the advent of on-site 'hotel' facilities, it remains to be seen whether such facilities will either cope with current problems or meet the growing demands of the future.

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Interventional radiology in the maintenance of infrainguinal vein graft patency

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The impact of interventional radiology on the cumulative patency rate of 112 consecutive infrainguinal vein grafts was reviewed. The primary, primary assisted and secondary cumulative patency rates at 42 months were 40, 65 and 69 per cent respectively. The difference between primary and primary assisted patency rates (40 versus *65 per cent,* $P = 0{\cdot}001$*) resulted from the early detection and treatment of stenoses in 30 grafts by percutaneous transluminal angioplasty (PTA). Interventional radiology also improved the cumulative graft patency rate through PTA of one inflow and five outflow arteries, thrombolysis of two graft occlusions, embolization of two persistent arteriovenous fistulas and salvage of one graft on the first day after operation by percutaneous aspiration of distal graft thrombus. Interventional radiology has a crucial role to play in the maintenance of infrainguinal vein graft patency; provided that graft stenoses are detected early in their development by aggressive graft surveillance, PTA is a highly effective treatment.*

Although it is generally agreed that autogenous vein is the conduit of choice for infragenicular bypass grafting[1,2], it is also recognized that about 30 per cent of grafts develop focal stenoses[3] and that once occluded these grafts are difficult to salvage[4]. Moreover, even if salvaged, occluded grafts have a disappointingly low cumulative patency rate[4]. In an attempt to detect and correct graft-threatening stenosis before occlusion, a programme of vein graft surveillance[5] was carried out; it was decided to treat vein graft stenoses in the first instance by percutaneous transluminal angioplasty (PTA). This paper describes the radiological techniques and results of this approach. The overall role of interventional radiology in the maintenance of infrainguinal vein graft patency is also reviewed.

Patients and methods

All infrainguinal vein grafts constructed during the period July 1988 to March 1992 were prospectively entered into a surveillance programme. The operative techniques have previously been detailed[2]. During the period of this study *in situ* vein grafts were exposed throughout their length and angioscopy was not used. Haemodynamically significant stenoses were treated by PTA as first-line therapy. Interventional radiological techniques were also used to perform angioplasty on stenosed inflow and outflow arteries, embolize persistent arteriovenous fistulas, salvage occluded grafts by thrombolysis and aspirate thrombus.

Vein graft surveillance[5]

Patients were examined during the first year after operation at 1, 3, 6, 9 and 12 months and thereafter at intervals of 6 months. Each visit consisted of a clinical assessment, measurement of systolic ankle: brachial pressure indices (ABPIs) before and after exercise and a duplex scan (Diasonics DRF 400 7·5-MHz probe; Diasonics Sonotron, Bedford, UK) of the entire graft. In the last year of the study the graft and distal tibial vessels were also insonated with a colour-coded duplex scanner (Diasonics Spectra). The criteria for requesting conventional arteriography were a clinical deterioration, a serial fall in resting ABPI $>0{\cdot}10$, a positive exercise test ABPI fall $>0{\cdot}10$ or a segmental duplex peak velocity ratio >3 (corresponding approximately to a >70 per cent reduction in cross-sectional area[6]). All stenoses detected by arteriography were treated in the first instance by PTA.

Radiological techniques

All procedures were carried out by a single consultant radiologist (A.B.). Diagnostic conventional arteriography was performed using a Seldinger technique via the contralateral groin. Therapeutic interventions were approached via the contralateral groin for lesions in the proximal third of a graft and via the ipsilateral groin for those in the distal two-thirds. Exceptions to this generalization were dictated by previous surgery and scarring. PTA of graft stenoses was performed antegradely using hydrophilic angled guidewires (Radiofocus; Terumo, Tokyo, Japan) with balloon catheters (Stellar 535; PSG, Mountain View, California, USA or Medi-tech Ultra-thin; Med-tech, Watertown, Massachusetts, USA) of the same diameter as the graft on the radiograph, allowing for a 15 per cent magnification. Dilators were not used. Stenoses were dilated with inflation pressures of up to 12 atmospheres for 30 s, repeated up to a total of three times as necessary. Patients received 150 mg oral aspirin immediately before angioplasty and a single intravenous bolus of heparin (5000 units) during the procedure. Aspirin was continued for 3 months after angioplasty. To minimize vessel spasm all patients received 12·5 mg intravenous tolazoline at the start and conclusion of the procedure. Intra-arterial glyceryl trinitrate (100-μg bolus repeated up to three times) was used to treat established vein graft or distal vessel spasm.

Inflow vessels were dilated using the techniques described above whereas distal run-off vessels underwent angioplasty using low-profile 3-mm balloons (Schneider Match-35; Schneider, Buelach, Switzerland). Thrombolysis was performed using a 5-Fr catheter (Softip; Schneider–Shiley, Minneapolis, Minnesota, USA) that was advanced through the thrombus and lodged distally, streptokinase then being infused at a rate of 5000 units/h and heparin intravenously at 500 units/h. The catheter was slowly withdrawn (1 cm every 15 min) and arteriography repeated at intervals of 4 h. Free thrombus was aspirated using a 5-Fr non-tapered curved-tip catheter (Radiofocus; Terumo) passed through an introducer sheath. Thrombolytic therapy was terminated when antegrade flow was established in the graft.

Embolization of persistent arteriovenous fistulas was performed via an introducer sheath in the ipsilateral groin using a 5-Fr curved-tip non-tapered catheter and 3-mm diameter 1-cm long stainless steel spring coils (W. Cook, Bjæverskov, Denmark).

Data analysis

Graft patency was assessed as recommended by Rutherford[7]. Primary patency was defined as uninterrupted patency with no procedures performed on the graft or its anastomoses. Assisted primary patency was defined as uninterrupted patency but allowed procedures to be performed on a patent bypass to prevent its eventual thrombosis. Secondary patency required that flow was restored through most of the original graft including at least one of its original anastomoses.

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Actuarial patency curves were computed (Systat package; Systat, London, UK) using the Kaplan–Meier[8] method and compared with the Mantel–Haenszel log rank test[9]. Discrete variables were analysed by the χ^2 test with Yates' correction.

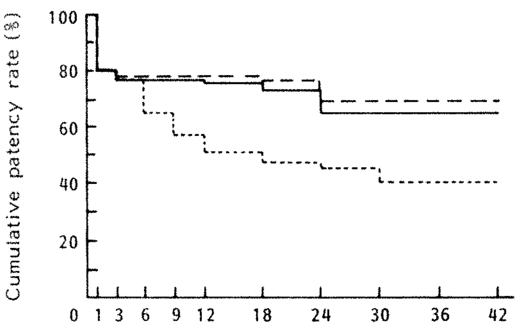
Results

A total of 112 infrainguinal vein grafts were performed on 106 patients during the 44-month study period. Patient and graft details are shown in *Table 1*. The median systolic ABPI in the 38 non-diabetic patients with rest pain or gangrene was 0·32 (range 0·00–0·74). Seventy-nine grafts (71 per cent) were *in situ*, 33 (29 per cent) were reversed; cumulative graft patency rates are shown in *Figure 1*. Of the grafts, 23 (20 per cent) had irreversibly occluded by 1 month and the primary, primary assisted and secondary patency rates at 42 months were 40, 65 and 69 per cent respectively. Five grafts occluded after 1 month (*Table 2*); in addition to the stenoses in two of the grafts that occluded, an additional 31 stenoses were revealed by graft surveillance. In total, therefore, 33 stenoses developed in 30 grafts (three grafts developed two stenoses at different sites) (*Table 3*). A total of eight stenoses were symptomatic (five claudicants, one gangrenous toe and two graft occlusions). It can be seen that 58 per cent of stenoses were detected and treated within the first 6 months after operation. The mean time from operation to treatment of stenosis was 7 (range 1–36) months. The majority of stenoses were located in the distal third of the grafts, half of these at the distal anastomosis (*Figures 2* and *3*); 94 per cent of stenoses were <2 cm in length (*Figure 4*).

Table 1 *Details of 112 infrainguinal vein grafts performed on 106 patients*

Median (range) age (years)	75 (32–97)
Sex ratio (M:F)	68:38
Indication*	
Claudication	15 (13)
Rest pain	38 (34)
Tissue necrosis	59 (53)
Graft type*	
In situ	79 (71)
Reversed	33 (29)
Graft position*	
Above-knee popliteal	6 (5)
Reversed	6 (100)
Below-knee popliteal	30 (27)
Reversed	8 (27)
Infrapopliteal (distal)	76 (68)
Reversed	19 (25)

*Values in parentheses are percentages



No. at risk

	0	1	3	6	9	12	18	24	30	36
Secondary	112	85	79	76	72	61	53	36	23	10
Primary assisted	112	85	79	76	70	60	51	35	25	10
Primary	112	85	76	62	52	39	31	19	16	8

Figure 1 *Cumulative primary (----), primary assisted (——) and secondary (– – –) graft patency rates. The s.e.m. is <10 per cent at all time points for the three curves.* P = *0·001 (primary* versus *primary assisted, log rank test)*

Table 3 *Details of the 33 graft stenoses that developed in 30 grafts*

Time of detection after operation (months)		
<6	19 (58)	
6–12	10 (30)	
>12	4 (12)	
Site		
Proximal anastomosis	2	8 (24)
Proximal third	6	
Middle third	7 (21)	
Distal third	9	18 (55)
Distal anastomosis	9	
Graft type*		
Reversed	8 of 33 (24)	
In situ	22 of 79 (28)	
Graft position†		
Above-knee popliteal	2 of 6 (33)	
Below-knee popliteal	8 of 30 (27)	
Infrapopliteal	20 of 76 (26)	
Length (cm)		
<2	31 (94)	
≥ 2	2 (6)	

Values in parentheses are percentages. $^*\chi^2 = 0{\cdot}15$, 1 d.f., $P = 0{\cdot}75$ (reversed *versus in situ*); $^\dagger\chi^2 = 0{\cdot}001$, 1 d.f., $P = 0{\cdot}98$ (below-knee popliteal *versus* infrapopliteal)

Table 2 *Details of the five grafts that occluded after 1 month*

Patient no.	Time after operation (months)	Reason for occlusion	Treatment	Outcome
1	4	Graft stenosis Failed to attend for surveillance	Thrombolysis and PTA	Patent Needed surgical revision
2	4	Surveillance showed no run-off vessels	None	Occluded Rest pain Simple analgesia
3	10	Unknown Failed to attend for surveillance	None	Occluded Rest pain Simple analgesia
4	14	Hypotension during myocardial infarction	None	Occluded No rest pain
5	16	Surveillance showed stenosis Occlusion occurred while awaiting PTA	Thrombolysis and PTA	Patent Needed surgical revision

PTA, percutaneous transluminal angioplasty

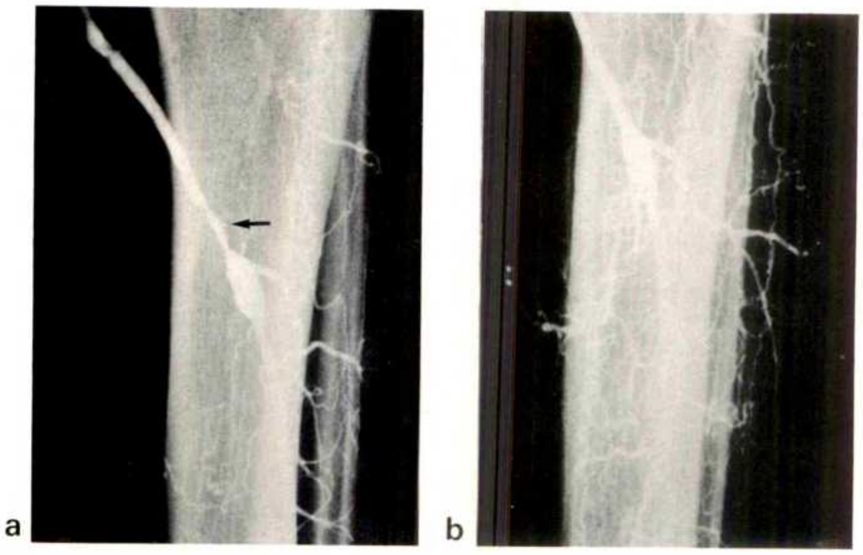


Figure 2 *Distal graft stenosis (arrow)* **a** *before and* **b** *after percutaneous transluminal angioplasty*

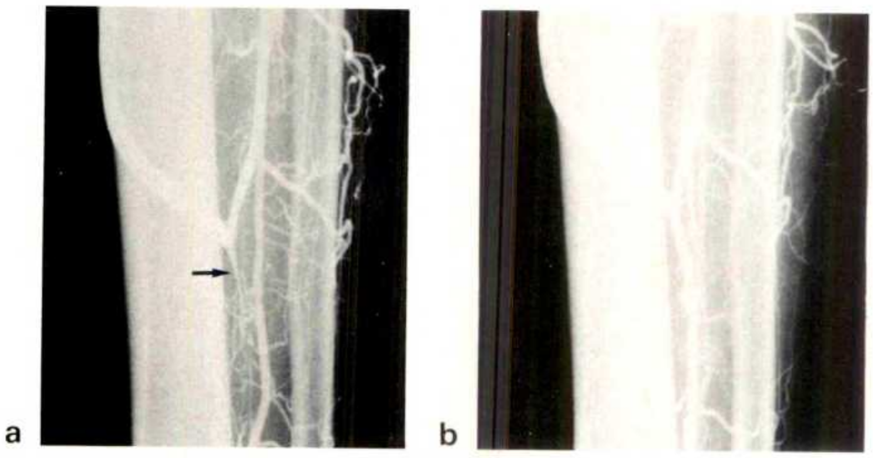


Figure 3 *Distal anastomotic stenosis (arrow)* **a** *before and* **b** *after percutaneous transluminal angioplasty*

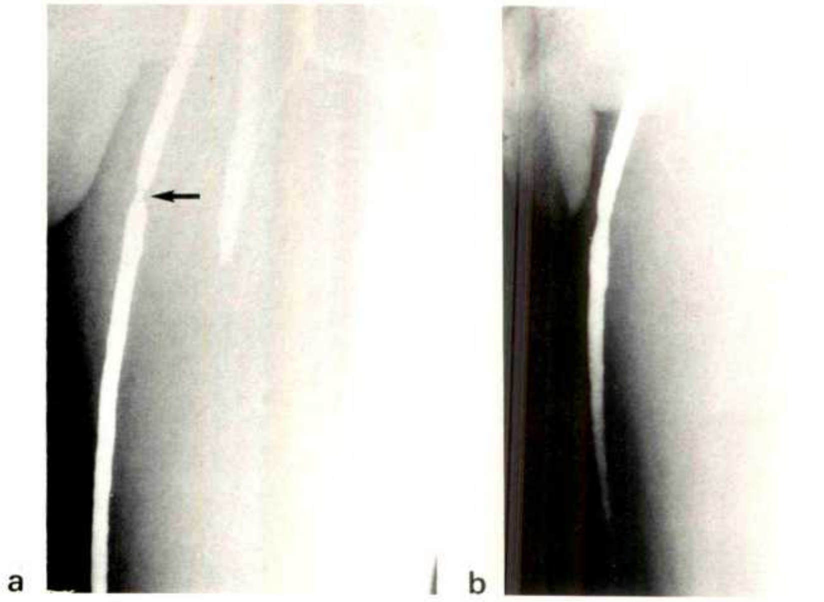


Figure 4 *Short stricture (arrow) in the proximal third of a graft* **a** *before and* **b** *after percutaneous transluminal angioplasty*

Angioplasty of graft stenoses

The results of graft stenosis angioplasty are shown in *Figure 5*. It can be seen that 23 of 33 stenoses (70 per cent) were successfully treated by a single dilatation. In all of these grafts the previously abnormal flow at the stenosis site returned to normal after angioplasty (no turbulence on duplex scan). Five grafts (15 per cent) required two PTA procedures; the second angioplasties were performed at 6, 10, 12, 13 and 16 months after the first dilatation. One graft underwent four angioplasties of the same stenosis that recurred at 2, 6 and 22 months because the patient was unfit for revisional surgery. Four stenoses were treated by revisional surgery; two were in patients who presented with graft occlusion (numbers 1 and 5 in *Table 2*) and these cases are discussed below. The indication for surgery in the other two patients was an unsatisfactory result after a second angioplasty of a distal stenosis.

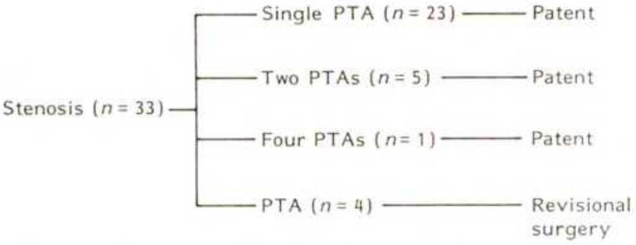


Figure 5 *Treatment of the 33 graft stenoses. PTA, percutaneous transluminal angioplasty*

The median follow-up for the 29 stenoses treated by PTA alone was 19 (range 1–40) months. Twelve of the 29 stenoses (41 per cent) had not recurred after at least 2 years' follow-up. The only complication from angioplasty of a graft stenosis was a distal embolization in one patient that required surgical embolectomy.

Thrombolysis of occluded grafts

Two of the grafts that occluded after 1 month were salvaged by thrombolysis (*Table 2*). In patient 1, thrombolysis of the graft revealed a distal stenosis that was partially treated by PTA. Within 2 h, however, the graft flow had reduced again and the distal 10 cm of the graft was therefore replaced. In patient 5, a distal stenosis had been detected by graft surveillance and angioplasty was arranged for 48 h later. Unfortunately, the graft occluded during this 48 h and was salvaged by thrombolysis and a partially successful PTA; 24 h later graft flow had reduced and the distal 8 cm of the graft was therefore surgically replaced.

Angioplasty of inflow and outflow vessels

One patient underwent PTA of an external iliac stenosis 7 days after operation. This stenosis was thought to be insignificant

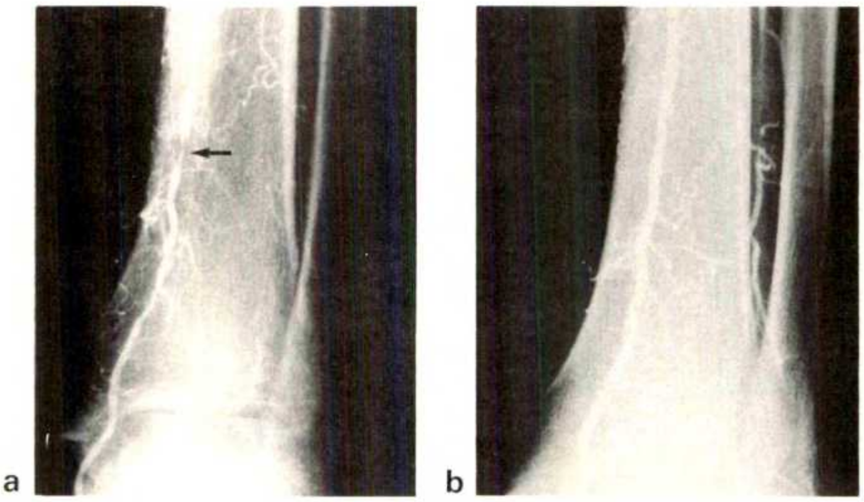


Figure 6 **a** *Tight stenosis (arrow) in the posterior tibial artery distal to a femorodistal graft;* **b** *after successful dilatation by percutaneous transluminal angioplasty*

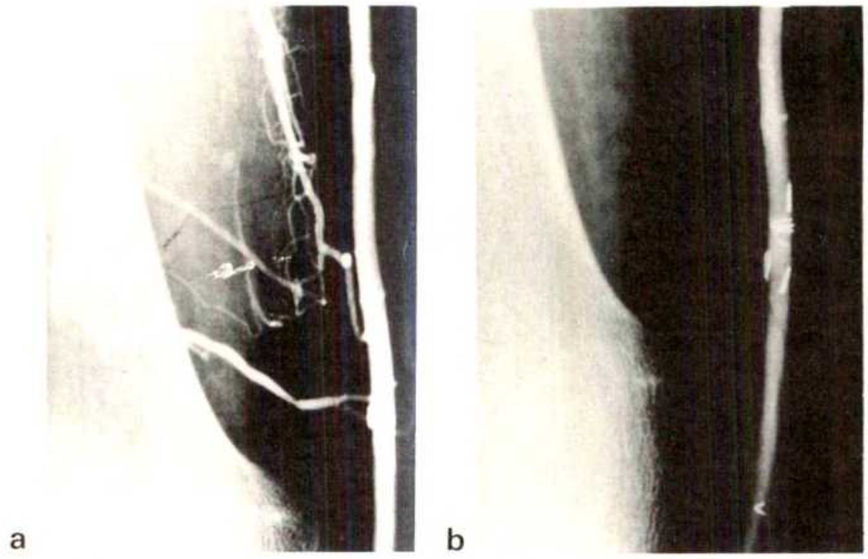


Figure 7 *Arteriogram* **a** *on the first day after operation showing arteriovenous fistulas;* **b** *after successful embolization*

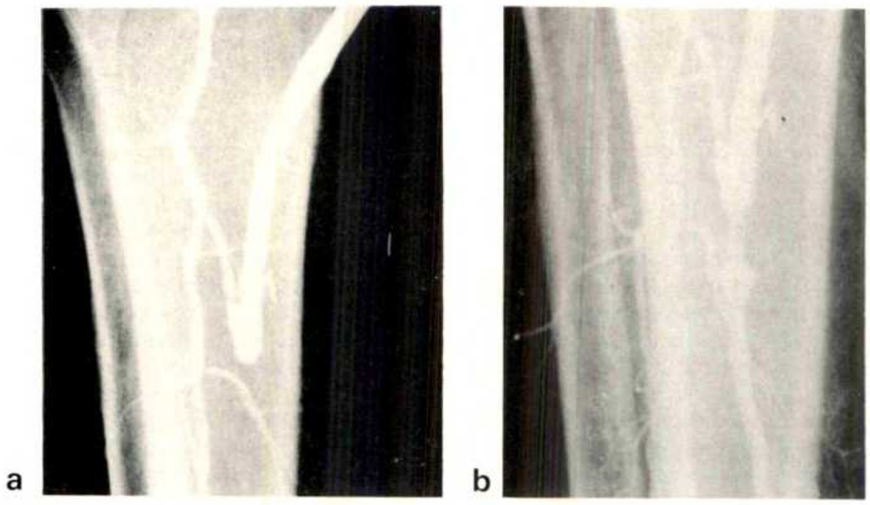


Figure 8 *Arteriogram* **a** *after embolization of arteriovenous fistula showing the distal anastomosis occluded by thrombus;* **b** *after successful aspiration*

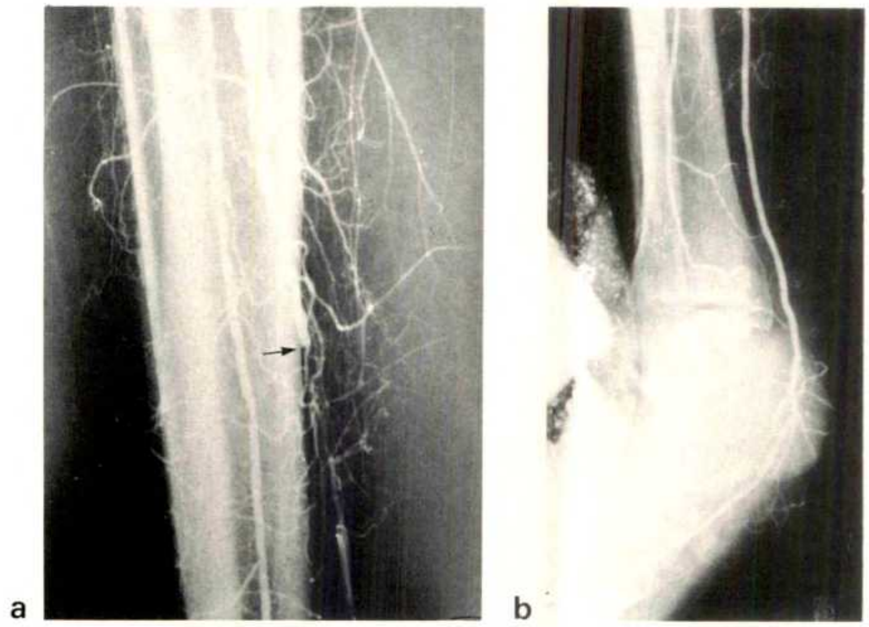


Figure 9 **a** *Occluded posterior tibial artery (arrow);* **b** *the thrombus was successfully aspirated and percutaneous transluminal angioplasty of a posterior tibial artery stenosis performed*

on preoperative arteriography; after PTA, however, the graft flow markedly improved. Five patients had distal calf vessels subjected to angioplasty, three in conjunction with PTA of a graft stenosis and two as the sole procedure (*Figure 6*).

Embolization of arteriovenous fistulas and thrombus aspiration

One patient was noted to have two patent arteriovenous fistulas at the time of PTA of a graft stenosis 3 months after operation; these fistulas were embolized without complication. A second patient with a femoroposterior tibial graft was noted on duplex examination on the first day after operation to have patent arteriovenous fistulas. Urgent arteriography confirmed four fistulas, which were embolized (*Figure 7*). The same arteriogram showed that the posterior tibial artery was occluded by thrombus at the level of the distal anastomosis; this thrombus was successfully aspirated (*Figure 8*). Some 16 days later it was noted that the ankle Doppler ultrasonography signal from the posterior tibial artery was damped and arteriography showed that this vessel was occluded below the distal anastomosis; further thrombus was aspirated and a stenosis of the posterior tibial artery treated by angioplasty (*Figure 9*). The graft was patent at review 6 months later.

Discussion

The impact of interventional radiology on infrainguinal vein graft patency can be seen by comparing the cumulative primary rate (40 per cent) and primary assisted patency rate (65 per cent) at 42 months. This difference, which is statistically significant ($P = 0{\cdot}001$), arises solely from the early detection and correction of graft stenoses by PTA. In addition, interventional radiology contributed to the difference between primary assisted and secondary patency rates (the latter 69 per cent) at 42 months through thrombolysis of two graft occlusions before surgery.

It is important to question whether all the graft stenosis angioplasties were necessary and whether all the asymptomatic stenoses would have progressed to graft occlusion. The only certain way to answer this would be to randomize asymptomatic stenoses to PTA or simple observation. However, in view of the literature describing the natural history of stenosis[10–12], the authors' experience and other reports of graft occlusion occurring during the period between detection of an asymptomatic stenosis and treatment[13,14], such a trial seems unethical. It is interesting to note, however, that before introduction of the present graft surveillance programme the primary patency rate at 42 months for infrainguinal vein grafts was 42 per cent[2], close to the present figure of 40 per cent. This strongly suggests that the majority of stenoses treated by PTA in the present study would have progressed to occlusion if left untreated.

Although there is a growing consensus that the early detection of asymptomatic infrainguinal vein graft stenosis by graft surveillance is worthwhile[3,10–15], there is disagreement whether stenoses are best treated by PTA[15–19] or surgical revision[20–25]. Berkowitz *et al.*[18] recently reported that 57 per cent of stenoses could be treated by a single PTA procedure (compared with the present figure of 70 per cent) and recommended 'balloon angioplasty as primary therapy for vein graft stenoses'. However, Whittemore *et al.*[25] concluded that 'balloon angioplasty for vein graft stenosis had significant limitations in providing sustained secondary patency'. Although Bandyk *et al.*[24] preferred surgical revision to PTA, they treated only five of 78 graft stenoses by angioplasty and did not formally compare the two techniques.

At first sight these disparate results are difficult to understand. Certainly there is no reason to think that the fundamental pathological lesion is different between centres; although Berkowitz *et al.*[18] reported solely on the results of treating stenoses in reversed grafts by PTA while others have treated stenoses in reversed and *in situ* grafts by angioplasty[16,19,23–25], the incidence of stenoses and the basic pathology is similar in the two graft types[26]. Similarly, the sites of stenosis and the angioplasty techniques used to treat them do not differ greatly between centres. It has been suggested that the length of stenosis may be important, with longer stenoses (>1 cm (Reference 27), >1·5 cm (Reference 28), >2 cm (Reference 29)) responding poorly to PTA. Although Berkowitz *et al.*[18] and Whittemore and colleagues[25] did not find that stenosis length affected outcome, it should be noted that the former group elected to treat all long stenoses (>5 cm) surgically, which may have reduced the significance of stenosis length on outcome after angioplasty. In the latter series, only 18 of 54 stenosis angioplasties were for single lesions in a graft[25]. The remainder were multiple graft lesions and so for any one graft occlusion it is not possible to know whether long or short stenoses led to occlusion.

That the majority of the present graft stenoses (94 per cent) were <2 cm long may have contributed to the good results from PTA. An important similarity between groups reporting good results from PTA[16–19,28] is that they tend to have an aggressive approach to graft surveillance and angioplasty of detected stenoses. This approach may lead to the detection and treatment of stenoses early in their development, perhaps before they become resistant to PTA. This hypothesis is consistent with short stenoses representing early lesions because it has been shown experimentally[30] that low flow predisposes to intimal hyperplasia and so a short localized stenosis might be expected to propagate distally with time as a result of turbulent low flow beyond it.

The potential importance of an aggressive approach to graft surveillance is illustrated by a comparison of the present policy with that of Whittemore *et al.*[25]. The authors regularly screen all infrainguinal vein grafts using as criteria a serial resting or postexercise ABPI drop >0·10 and/or a segmental duplex peak velocity ratio >3. The high sensitivity (100 per cent) of a serial resting ABPI drop >0·10 has recently been confirmed by Stierli *et al.*[31]. As a consequence of this policy only 24 per cent of stenoses were symptomatic at the time of PTA; the mean time after operation to angioplasty was 7 months and only 6 per cent of stenoses presented as occlusions. By comparison, all the patients reported by Whittemore *et al.*[25] were symptomatic, the mean time to PTA was 18 months and 20 per cent of stenoses presented as occlusions. Further support for the hypothesis that an aggressive graft surveillance policy results in lesions being treated early in their development comes from the observation that all of the present technically successful angioplasties had <10 per cent residual stenosis on post-PTA arteriography whereas Whittemore *et al.*[25] reported a mean residual stenosis rate of 22 per cent.

Only one patient has required PTA of a graft inflow artery; this is because the majority of significant inflow disease is treated by angioplasty during the initial preoperative arteriography. Five patients, however, have required PTA of distal calf vessels. The number of patients requiring distal PTA might be expected to increase with longer follow-up, and colour-coded duplex scanning may prove particularly advantageous in the non-invasive assessment of distal calf vessel disease.

The role of thrombolytic therapy for occluded infrainguinal vein grafts has been the source of debate[32,33]. Although the authors' experience of the technique is too limited to draw any firm conclusions of the benefits, the theoretical advantages seem attractive[32]. These include the demonstration of intrinsic graft lesions by arteriography before surgery or PTA, lysis of thrombus in the distal run-off vessels and avoidance of mechanically induced balloon-catheter trauma. It is agreed with Seabrook *et al.*[34] that graft thrombolysis can be expected to produce good results only if run-off vessel defects revealed by clot lysis are corrected promptly.

Persistent arteriovenous fistulas are unique to *in situ* grafts and may be asymptomatic, cause persistent oedema or result in ischaemia and even distal graft thrombosis[35]. They can be either ligated under local anaesthesia[36] or embolized with a detachable balloon[37] or coil[38]. Both affected patients were treated by embolization because they required arteriography for other reasons. The second patient provided a salutary experience because it was apparent that the fistulas were keeping the proximal graft patent in the face of a distal occlusive lesion. Before fistula ligation the patency of the distal vasculature should therefore be confirmed by non-invasive techniques.

In conclusion, interventional radiology has a crucial role to play in the maintenance of infrainguinal vein graft patency. PTA is a highly effective treatment for vein graft stenoses provided they are detected early in their development by aggressive surveillance. Finally, the authors agree with Veith *et al.*[16] that detected stenoses should be treated as a matter of urgency.

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References

1. Londrey LG, Ramsey DE, Hodgson KJ, Barkmeier LD, Sumner DS. Infrapopliteal bypass for severe ischaemia: comparison of autogenous vein, composite, and prosthetic grafts. *J Vasc Surg* 1991; **13**: 631–6.
2. Budd JS, Brennan J, Beard JD, Warren H, Burton PT, Bell PRF. Infrainguinal bypass surgery: factors determining late graft patency. *Br J Surg* 1990; **77**: 1382–7.
3. Harris PL. Vein graft surveillance – all part of the service. *Br J Surg* 1992; **79**: 97–8.
4. Belkin M, Donaldson MC, Whittemore AD *et al.* Observations on the use of thrombolytic agents for thrombotic occlusion of infrainguinal vein grafts. *J Vasc Surg* 1990; **11**: 289–96.
5. Brennan JA, Walsh AKM, Beard JD, Bolia AA, Bell PRF. The role of simple non-invasive testing in infrainguinal vein graft surveillance. *Eur J Vasc Surg* 1991; **5**: 13–17.
6. Spencer MP, Reid JM. Quantification of carotid stenosis with continuous-wave (C-W) Doppler ultrasound. *Stroke* 1979; **10**: 326–30.
7. Rutherford RB. Standards for evaluating results of interventional therapy for peripheral vascular disease. *Circulation* 1991; **83**(Suppl I): I6–11.
8. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–81.
9. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; **22**: 719–48.
10. Moody P, DeCossart LM, Douglas HM, Harris PL.

Asymptomatic strictures in femoro-popliteal vein grafts. *Eur J Vasc Surg* 1989; **3**: 389–92.

11. Grigg MJ, Nicolaides AN, Wolfe JHN. Femorodistal vein bypass graft stenoses. *Br J Surg* 1988; **75**: 737–40.
12. Green RM, McNamara J, Ouriel K, De Weese JA. Comparison of infrainguinal graft surveillance techniques. *J Vasc Surg* 1990; **11**: 207–15.
13. Taylor PR, Wolfe JHN, Tyrrell MR, Mansfield AO, Nicolaides AN, Houston RE. Graft stenosis: justification for 1 year surveillance. *Br J Surg* 1990; **77**: 1125–8.
14. Buth J, Disselhoff B, Sommeling C, Stam L. Colour flow duplex criteria for grading stenosis in infrainguinal vein grafts. *J Vasc Surg* 1991; **14**: 716–28.
15. Berkowitz HD, Greenstein S, Barker CF, Perloff LJ. Late failure of reversed vein bypass grafts. *Ann Surg* 1989; **210**: 782–6.
16. Veith FJ, Weiser RK, Gupta SK *et al.* Diagnosis and management of failing lower extremity arterial reconstructions prior to graft occlusion. *J Cardiovasc Surg* (*Torino*) 1984; **25**: 381–4.
17. Berkowitz HD, Greenstein SM. Improved patency in reversed infrapopliteal autogenous vein grafts by early detection and treatment of the failing graft. *J Vasc Surg* 1987; **5**: 755–61.
18. Berkowitz HD, Fox AD, Denton DH. Reversed vein graft stenoses: early detection and management. *J Vasc Surg* 1992; **15**: 130–42.
19. Moody P, Gould DA, Harris PL. Vein graft surveillance improves patency in femoro-popliteal bypass. *Eur J Vasc Surg* 1990; **4**: 117–21.
20. Cohen JR, Mannick JA, Couch NP, Whittemore AD. Recognition and management of impending vein graft failure. *Arch Surg* 1986; **121**: 758–9.
21. Thompson JF, McShane MD, Gazzard V, Clifford PC, Chant ADB. Limitations of percutaneous transluminal angioplasty in the treatment of femorodistal graft stenoses. *Eur J Vasc Surg* 1989; **3**: 209–11.
22. Thompson JF, McShane MD, Clifford PC, Gazzard V, Webster JH, Chant ADB. Intervention for graft stenoses: the role of surgery and transluminal angioplasty. *Br J Surg* 1989; **76**: 1017.
23. Perler BA, Osterman FA, Mitchell SE, Burdick JF, Williams GM. Balloon dilatation *versus* surgical revision of infrainguinal autogenous vein graft stenoses: long-term follow-up. *J Cardiovasc Surg* (*Torino*) 1990; **31**: 656–61.
24. Bandyk DF, Bergamini TM, Towne JB, Schmitt DD, Seabrook GR. Durability of vein graft revision: the outcome of secondary procedures. *J Vasc Surg* 1991; **13**: 200–10.
25. Whittemore AD, Donaldson MC, Polak JF, Mannick JA. Limitations of balloon angioplasty for vein graft stenosis. *J Vasc Surg* 1991; **14**: 340–5.
26. Wengerter KR, Veith FJ, Gupta SK *et al.* Prospective randomized multicenter comparison of *in-situ* and reversed infrapopliteal bypasses. *J Vasc Surg* 1991; **13**: 189–99.
27. Taylor PR, Gould D, Harris PL, Al-Kutoubi A, Wolfe JH. Balloon dilatation of graft stenoses – reasons for failure. *Br J Surg* 1991; **78**: 371 (Abstract).
28. Sanchez LA, Gupta SK, Veith FJ *et al.* A ten-year experience with one hundred fifty failing or threatened vein and polytetrafluoroethylene arterial bypass grafts. *J Vasc Surg* 1991; **14**: 729–38.
29. Harris PL, Moody AP. The management of vein bypass stricture. In: Greenhalgh RM, Hollier LH, eds. *The Maintenance of Arterial Reconstruction.* London: WB Saunders, 1991: 169–78.
30. Dobrin PB, Litooy FN, Litooy ED. Mechanical factors predisposing to intimal hyperplasia and medial thickening in autogenous vein grafts. *Surgery* 1989; **105**: 393–400.
31. Stierli P, Aeberhard P, Livers M. The role of colour flow duplex screening in infrainguinal vein grafts. *Eur J Vasc Surg* 1992; **6**: 293–8.
32. Belkin M, Donaldson MC, Whittemore AD *et al.* Observations on the use of thrombolytic agents for thrombotic occlusion of infrainguinal vein grafts. *J Vasc Surg* 1990; **11**: 289–96.
33. Bandyk DF, Towne JB, Schmitt DD, Seabrook GR, Bergamini TM. Therapeutic options for acute thrombosed *in-situ* saphenous vein arterial bypass grafts. *J Vasc Surg* 1990; **11**: 680–7.
34. Seabrook GR, Mewissen MW, Schmitt DD *et al.* Percutaneous intraarterial thrombolysis in the treatment of thrombosis of lower extremity arterial reconstructions. *J Vasc Surg* 1991; **13**: 646–51.
35. Kalman PG, Sniderman KW. Salvage of *in-situ* femoropopliteal and femorotibial vein bypass with interventional radiology. *J Vasc Surg* 1988; **4**: 429–32.
36. Cullen PJ, Lehay AL, Ryan SB, McBride KO, Moore DJ, Shanik GD. The influence of duplex scanning on early patency rates of *in-situ* bypass to the tibial vessels. *Ann Vasc Surg* 1986; **1**: 340–6.
37. Kinnison ML, Perler BA, Kaufman SL *et al.* *In-situ* saphenous vein bypass grafts: angiographic evaluation and interventional repair of complications. *Radiology* 1986; **160**: 727–30.
38. Sniderman KW, Kalman PG, Shewchun J, Goldberg REA. Lower extremity *in-situ* saphenous vein grafts: angiographic interventions. *Radiology* 1989; **170**: 1023–7.

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Early results and 1-year follow-up after intra-arterial thrombolysis

Intra-arterial thrombolysis (IAT) was used as first-line treatment for 100 occlusions causing acute, subacute or chronic ischaemia. Streptokinase was used in 90 cases and tissue plasminogen activator in the remaining ten. Complete lysis, as determined radiologically, was achieved in 55 per cent of cases and partial lysis in 20 per cent. Lysis was more effective the earlier it was used. Major complications occurred in seven cases: five patients suffered major haemorrhage, two of whom died, and two had haemorrhagic cerebrovascular accidents. Of the patients with complete or partial clearance of thrombosis, 19 had no underlying apparent cause, 23 underwent angioplasty and 15 had an operation. The 1-year patency rate following complete lysis was 58 per cent. The 1-year patency rate after successful treatment commencing within 1 week of symptoms starting was 71 per cent, compared with 36 per cent for later treatment. Aortofemoral bifurcation grafts were cleared in three of five cases and all remain patent. Eight popliteal aneurysms were demonstrated by IAT and were ligated and bypassed; all these grafts remained patent at follow-up. IAT is less effective in chronic than acute occlusion. It should be reserved for patients in whom the occlusion is of short duration or for those with a thrombosed aortofemoral bifurcation graft or popliteal aneurysm.

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The role of intra-arterial thrombolysis (IAT) in the treatment of acute and chronic arterial occlusion remains unclear. Recent surveys of the practice of vascular surgeons in the UK confirmed that few centres had wide experience of the technique, the main reasons for which were lack of radiological support, doubts about efficacy, and insufficient ward staff[1]. Despite this, 50 per cent of surgeons had tried thrombolysis[2], although most had experience of only a few cases per year.

Successful clearance of acute embolus and thrombosis occurs in 50–90 per cent of cases[3,4] and, even with occlusion of longer duration, reasonable results have been reported. Hess and colleagues[5] and Lammer *et al.*[6] found IAT useful in thrombus of up to 6 months' duration, but the results worsened after this time. More recent reports have suggested that any non-organized thrombus may be lysed[7]. The reported complications of this type of treatment have recently been reviewed[8]. Major haemorrhage occurs in 5 per cent of cases, stroke in 1 per cent and minor haemorrhage and catheter-related problems in approximately 15 per cent.

This paper describes the early and 1-year results achieved in this unit with IAT. An attempt is made to define patients for whom the technique is appropriate and those for whom other forms of treatment may be better.

Patients and methods

IAT was carried out using a continuous infusion of lysing agent through a 5–7-Fr catheter. Access was generally through the ipsilateral femoral artery for distal occlusion, the contralateral femoral artery for common femoral or distal iliac occlusion, and the axillary artery for suprainguinal occlusion. Streptokinase (10000 units/h for the first 20 patients and subsequently 5000 units/h) and 0·5 mg/h recombinant human tissue-type plasminogen activator (rtPA; Boehringer Ingelheim, Bracknell, UK) were the agents used. Streptokinase was employed on 90 occasions and rtPA on ten. The latter was used only if the patient had received streptokinase within the previous 6 months. Angiography was performed through the cannula at intervals of 8–12 h. Manipulation of the catheter was carried out if necessary to maintain its position within the thrombus or embolus. Infusion was stopped if there was no progression of lysis over a 12-h period, if lysis was complete, or if a major complication occurred. Contraindications to IAT included dyspepsia, known haemorrhagic problems, recent operation, or history of cerebrovascular accident or transient ischaemic attack within 6 months.

Between November 1988 and April 1991, IAT was considered on 108 occasions for 100 patients. Eight patients did not receive the thrombolytic agent. In four of these the catheter could not be sited correctly. In one of the remainder, angioplasty was performed after assessment. One more died before treatment could start and one had a cerebrovascular accident during initial angiography. The final patient experienced severe abdominal pain while the catheter was being manipulated through the aorta; the procedure was abandoned and at laparotomy an infarcted caecum was resected. The patient died from renal and respiratory failure 3 days later. Four patients underwent lysis on two separate occasions; four others had IAT performed on separate lesions simultaneously. Three of these patients have been described previously[9]. Some 92 patients therefore underwent 100 episodes of IAT. The median age was 68 (range 42–89) years and the male:female ratio 3:1.

There were 80 thromboses (eight popliteal aneurysms, 16 grafts, 56 native arteries), producing rest pain in 48 and incapacitating intermittent claudication in 32. There were 11 cases of thrombosis or emboli following angioplasty. Nine other cases were caused by emboli from a cardiac source, the latter being confirmed by echocardiography. None of these patients had a neurological deficit at the time of treatment. The site of occlusion was generally below the inguinal

Table 1 *Site of 100 arterial occlusions treated with thrombolysis*

	No.
Brachial	5
Aortic	1
Iliac	4
Femoral	50
Popliteal	19
Distal	5
Grafts	
Aortofemoral	5
Infrainguinal	11

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ligament (*Table 1*). Following successful lysis, patients were assessed at intervals of 3 months. Patency was determined by clinical assessment and Doppler ultrasonography, confirmed by angiography as appropriate. Assessment of the long-term results was by Cutler–Ederer life-table survival curves with Mantel–Haenzel statistical analysis.

Results

IAT was started on 100 occasions and lysis achieved on 75. Radiological clearance was complete in 55 cases and partial in 20. Thrombolysis was more likely to be successful the earlier it was used (*Figure 1*). This applied particularly to complete clearance, which was obtained in 66, 50 and 35 per cent of cases if treatment was started during the first week, 1–4 weeks and >4 weeks after the development of symptoms respectively ($\chi^2 = 5{\cdot}5$, 1 d.f., $P < 0{\cdot}02$).

As might be expected, the best results were obtained with embolus. Successful lysis was achieved in all nine cases, patency being maintained at the time of follow-up. There was no significant difference in achieving complete radiological clearance between patients presenting with claudication and those with rest pain (47 *versus* 54 per cent respectively). No further treatment was required in the nine patients with acute embolus and in nine of those with embolus or thrombosis following angioplasty. Of the remainder, no treatable cause for the thrombosis was found in 19, angioplasty was performed in 23 and an operation in 15. On subsequent analysis there was no significant difference in the later results of these three groups.

Complications occurred in 36 patients; the majority were clinically insignificant (*Table 2*). Haemorrhage was defined as major if >2 units blood were transfused or if the systolic blood pressure dropped below 100 mmHg. Major haemorrhage occurred in five patients. In one, bleeding stopped on discontinuing thrombolysis, but four required surgical intervention to stop bleeding from the perfusing catheter puncture site. Two of these patients subsequently died. Two patients suffered stroke attributable to IAT; computed tomography confirmed both strokes to be haemorrhagic. One of these patients died. Minor haemorrhage in the form of wound haematoma or gastrointestinal bleeding was treated conservatively without further problems. Of the nine patients requiring cannulation of the axillary artery, extensive bruising of the arm occurred in three.

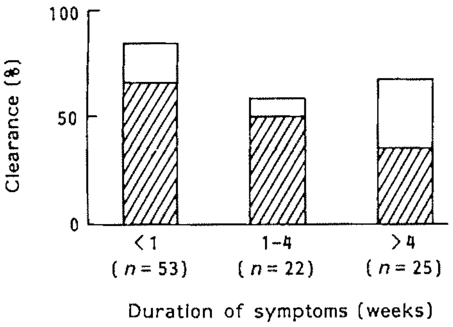
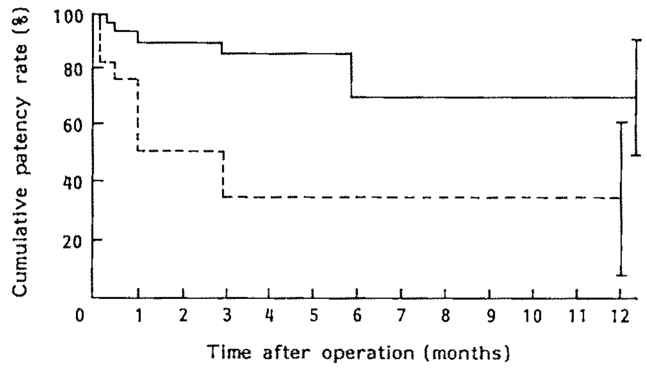


Figure 1 *Early results of thrombolysis.* ■, *Complete clearance;* □, *partial clearance*

Table 2 *Complications of thrombolysis*

	Fatal	Non-fatal	Total
Major			
Bleeding	2	3	5
Stroke	1	1	2
Minor			
Bleeding	—	23	23
Allergic reaction to streptokinase	—	2	2
Catheter breakage	—	2	2
Catheter kink	—	1	1
Catheter sepsis	—	1	1



No. at risk

≤1 week	31	26	23	18	11
>1 week	18	12	7	4	2

Figure 2 *Long-term patency rates in patients treated within 1 week of symptoms starting (—) and those treated >1 week after symptoms starting (---) Bars are 2 s.d.*

Thirteen patients died. Three deaths were attributable to IAT (one from cerebrovascular accident, two from bleeding). All these patients suffered from rest pain. The remaining deaths were from cardiopulmonary causes. Major amputation was performed in ten patients, all of whom had presented with rest pain. In eight, lysis had failed and only two were treated within 1 week of onset of symptoms.

Complete clearance resulted in a 1-year patency rate of 71 per cent in patients having thrombosis treated within 1 week of symptoms starting. By contrast, the 1-year patency rate was only 36 per cent for patients with symptoms of longer duration ($P < 0{\cdot}01$) (*Figure 2*). When combined with the higher early clearance rate, this means that 50 per cent of all occlusions originally treated acutely remained patent at 1 year, compared with only 15 per cent of those treated later.

When only partial radiological lysis was achieved, the long-term results were poor as most vessels rethrombosed early. In those partially cleared within the first week of symptoms, four of ten remain patent, at 3, 5, 11 and 29 months. However, in patients with longer duration of symptoms, all treated vessels rethrombosed by 4 months. Despite this, half of the patients were symptomatically improved, presumably because of clearance of collateral vessels. Only three patients in this group left hospital completely without symptoms. Although the patency rate was higher in patients with good run-off, this difference was not statistically significant.

Following rethrombosis of a completely lysed occlusion a wide spectrum of treatment was employed, including angioplasty (two cases), angioplasty and operation (one), operation (five), conservative treatment (three), and sympathectomy (one). Repeat thrombolysis was performed in four cases, of which three were successful with no additional treatment; the other required operation.

The brachial occlusions were all caused by emboli. In four the catheter was sited successfully and complete clearance achieved. The main problem with treating these lesions by lysis has been satisfactory placement of the catheter, the latter being inserted through a femoral artery approach[10].

Of the 16 thrombosed grafts treated, successful lysis was achieved in ten[11].

Certain patients with longstanding symptoms seem to have a more favourable outcome, including those with aortofemoral bypass graft thrombosis[11] or popliteal aneurysm[12]. Three of five thrombosed aortofemoral grafts were cleared and remain patent nearly 1 year later. Eight thrombosed popliteal aneurysms were treated; seven were completely cleared with good run-off and the other partially cleared. All grafts remain patent after ligation and bypass of the aneurysm.

Discussion

Patients presenting with acute limb ischaemia are now more likely to have a thrombotic occlusion of pre-existing arterial disease than an embolus[13]. The rate of limb loss is greater with thrombotic than embolic occlusion, but the mortality rate is higher with the latter[14]. IAT has the advantage over catheter embolectomy or thrombectomy that underlying disease can be identified and treated once the vessels are cleared. More of the run-off and collateral circulation may also be cleared. IAT may also produce less intimal damage than catheter embolectomy. This should result in improved mortality and amputation rates[15,16].

IAT is effective in clearing both native arteries and grafts. Though the early results are similar, patency is better maintained with the former[17]. Grafts above the inguinal ligament are more likely to be successfully cleared than those below it[11]. IAT is clearly more effective if used earlier rather than later. Nevertheless, successful lysis has been demonstrated[6] in thrombosis that has been present for up to 9 months and beyond, although with decreasing success[5]. In this unit the authors[12] have successfully cleared popliteal aneurysms that have been occluded for up to 2 years.

IAT has recently been shown to produce results better than operation, both in the management of acute thrombosis without neurological deficit[14] and in acute graft occlusion[18]. Successful treatment, both early and late, is dependent on treatment of underlying stenosis[19], the adequacy of run-off[20], and the length of the original occlusion[15]. The present study confirms that complete or partial radiological clearance can be achieved in up to 75 per cent of cases, depending on the duration of occlusion. The importance of the age of the occlusion has been emphasized by others. For example, in a series of thrombotic occlusions, 73 per cent of those under 6 months old were cleared compared with only 50 per cent of those of longer duration; lysis of embolus was more successful than that of thrombosis[16]. Rethrombosis within the first few weeks of successful lysis is common, and may occur in up to one-quarter of cases[16]. Some of these can be successfully treated again by lysis. Early rethrombosis is particularly common in patients with only partial radiological clearance; this is especially so if the occlusion is of long duration. It is possible that anticoagulation may be of benefit in these cases if no treatable underlying cause for the thrombosis is found.

This study has shown that 50 per cent of all acute occlusions treated remain patent at 1 year. However, in patients treated after >1 week of commencement of symptoms, patency is not maintained, making IAT a treatment of high risk with limited benefit. Interestingly, the main reason for the difference at 1 year is the rethrombosis rate within the first few weeks of successful lysis. Only about 10 per cent of the acutely occluded arteries rethrombose during this time compared with 50 per cent of those occluded for a longer period.

IAT for peripheral arterial occlusion is more effective than administration of either streptokinase[21] or rtPA[22] intravenously. The best lytic agent has yet to be established, although rtPA has the theoretical advantage, being fibrin-specific, of fewer systemic haematological effects. There is some evidence that rtPA may be better than streptokinase in peripheral arterial lysis[22]; it certainly acts more quickly[23]. However, the systemic use of rtPA for coronary artery occlusion appears to be associated with more complications than that of streptokinase[24]. The limited experience with rtPA in this series is too small to draw any definite conclusions with regard to either speed of action or safety. Larger studies are needed.

Radiological assessment (as complete or partial lysis) allied with clinical improvement is a useful means of assessing results. However, it is appreciated that in comparing one series with another a uniform means of assessment is essential. The type of evaluation described by the Nottingham group would appear particularly useful in this context[23].

Further refinements of IAT continue. Multiple-hole catheters, small catheters, 'vibration' techniques, mechanical thrombolysis and pulsed-spray thrombolysis have all been described[7,25]. Complication rates are likely to fall as shorter times to lysis are obtained with these techniques.

In conclusion, IAT should now be considered as a first-line treatment for acute thrombosis and embolism without neurological deficit. However, for longstanding occlusion the risks outweigh the benefits. Until more rapid lysis techniques are developed, IAT in such circumstances should be restricted to those in whom a good result can be predicted, namely patients with a thrombosed popliteal aneurysm or aortofemoral bifurcation graft.

References

1. Browse DJ, Torrie EPH, Galland RB. Limitations to the widespread usage of low-dose intra-arterial thrombolysis. *Eur J Vasc Surg* 1991; **5**: 445–9.
2. Earnshaw JJ, Shaw JFL. Survey of the use of thrombolysis for acute ischaemia in the UK and Ireland. *Br J Surg* 1990; **77**: 1041–2.
3. Barr H, Lancashire MJR, Torrie EPH, Galland RB. Intra-arterial thrombolytic therapy in the management of acute and chronic limb ischaemia. *Br J Surg* 1991; **78**: 284–7.
4. Walker WJ, Giddings AEB. A protocol for the safe treatment of acute lower limb ischaemia with intra-arterial streptokinase and surgery. *Br J Surg* 1988; **75**: 1189–92.
5. Hess H, Ingrisch H, Ninerasch KA, Rath H. Local low-dose thrombolytic therapy of peripheral arterial occlusions. *N Engl J Med* 1982; **307**: 1627–30.
6. Lammer J, Pilger E, Neuwmayer K, Schreyer H. Intraarterial fibrinolysis: long term results. *Radiology* 1986; **161**: 159–63.
7. Bookstein JJ, Fellmet B, Roberts A, Valji K, Davis G, Machado T. Pulsed-spray pharmacomechanical thrombolysis: preliminary clinical results. *AJR Am J Roentgenol* 1989; **152**: 1097–100.
8. Berridge DC, Makin GS, Hopkinson BR. Local low dose intra-arterial thrombolytic therapy: the risk of stroke or major haemorrhage. *Br J Surg* 1989; **76**: 1230–3.
9. Barr H, Torrie EPH, Galland RB. Management of synchronous arterial occlusions using intra-arterial thrombolysis. *Ann R Coll Surg Engl* 1992; **74**: 29–30.
10. Michaels JA, Torrie EPH, Galland RB. The treatment of upper limb vascular occlusions using intra-arterial thrombolysis. *Eur J Vasc Surg* 1993 (in press).
11. Browse DJ, Torrie EPH, Galland RB. Low-dose intra-arterial thrombolysis in the treatment of occluded vascular grafts. *Br J Surg* 1992; **79**: 86–8.
12. Lancashire MRJ, Torrie EPH, Galland RB. Popliteal aneurysms identified by intra-arterial streptokinase: a changing pattern of presentation. *Br J Surg* 1990; **77**: 1388–90.
13. Ljungman C, Adami HO, Bergqvist D, Berglund A, Persson I. Time trends in incidence rates of acute, non-traumatic extremity ischaemia: a population-based study during a 19-year period. *Br J Surg* 1991; **78**: 857–60.
14. Earnshaw JJ, Gregson RHS, Makin GS, Hopkinson BR. Acute peripheral arterial ischaemia: a prospective evaluation of differential management with surgery or thrombolysis. *Ann Vasc Surg* 1989; **3**: 374–9.
15. McNamara TO, Bomberger RA, Merchant RF. Intra-arterial urokinase as the initial therapy for acutely ischaemic lower limbs. *Circulation* 1991; **83**(Suppl I): I-106–I-119.
16. Hess H, Mietaschk A, Bruckl R. Peripheral arterial occlusions: a 6-year experience with local low-dose thrombolytic therapy. *Radiology* 1987; **163**: 753–8.
17. McNamara TO, Bomberger RA. Factors affecting initial and 6 month patency rates after intraarterial thrombolysis with high dose urokinase. *Am J Surg* 1986; **152**: 709–12.
18. Graor RA, Risius B, Young JR *et al.* Thrombolysis of peripheral arterial bypass grafts. Surgical thrombectomy compared with thrombolysis. *J Vasc Surg* 1988; **7**: 347–55.
19. Gardiner GA Jr, Harrington DP, Koltun W, Whitmore A, Merrick JA, Levin DC. Salvage of occluded arterial bypass grafts by means of thrombolysis. *J Vasc Surg* 1989; **9**: 426–31.
20. Scott DJA, Wyatt MG, Wilson YG, Murphy P, Baird RN, Horrocks M. Intra-arterial streptokinase infusion in acute lower limb ischaemia. *Br J Surg* 1991; **78**: 732–4.
21. Earnshaw JJ. Thrombolytic therapy in the management of acute limb ischaemia. *Br J Surg* 1991; **78**: 261–9.

22. Berridge DC, Gregson RHS, Hopkinson BR, Makin GS. Randomized trial of intra-arterial recombinant tissue plasminogen activator, intravenous recombinant tissue plasminogen activator and intra-arterial streptokinase in peripheral arterial thrombolysis. *Br J Surg* 1991; **78**: 988–95.
23. Lonsdale RJ, Berridge DC, Earnshaw JJ *et al.* Recombinant tissue-type plasminogen activator is superior to streptokinase for local intra-arterial thrombolysis. *Br J Surg* 1992; **79**: 272–5.
24. O'Donnell M. Battle of the clotbusters. *BMJ* 1991; **302**: 1259–61.
25. Schmitz-Rode T, Gunther RW. Percutaneous mechanical thrombolysis. A comparative study of various rotational catheter systems. *Invest Radiol* 1991; **26**: 557–63.

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Announcement

International Society of Surgery

The International Society of Surgery/Société Internationale de Chirurgie (ISS–SIC) is one of the oldest international societies in the world. It is integrated with many other societies including the International Association of Endocrine Surgeons and the International Association for the Society of Trauma and Surgical Intensive Care. The Society holds its International Surgical Week from 22–27 August 1993 in Hong Kong. There are numerous other participating societies and the organization of these biennial meetings is first class.

The British Section meets in the intervening year, and welcomes members of every surgical discipline. If anyone is interested in joining, please contact the representative of the British Section: Mr J. E. Clegg, Leighton Hospital, Middlewich Road, Crewe, Cheshire CW1 4QJ, UK.

J. F. Clegg

Br. J. Surg. 1993, Vol. 80, February, 198–200

Effect of foot compression on the velocity and volume of blood flow in the deep veins

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The A-V Impulse System reduces the incidence of deep vein thrombosis by pneumatically compressing the venae comitantes of the lateral plantar artery, causing an increase in the velocity of blood in the proximal axial veins. Using a duplex scanner the effects of altering the pressure, pulse duration and frequency of foot compression on the velocity and volume of blood flow in the superficial femoral and popliteal veins were quantified. In 20 legs, foot compression of 50, 125 and 200 mmHg significantly increased the maximum venous blood flow by 9·0, 13·4 and 15·1 ml/s respectively ($P < 0{\cdot}001$)*. Conversely, reducing the frequency of compression from 6 to 3 cycles per min significantly increased the rise in peak flow from 10·1 to 14·8 ml/s* ($P < 0{\cdot}001$)*. Changing the duration of compression from 1 to 3 s had no significant effect on peak flow. Increased blood flow is best achieved with high-pressure low-frequency foot compression. Increasing the duration of compression beyond 1 s has no effect on augmentation of flow in the deep veins.*

Gardner and Fox[1,2] have described how compression of the venae comitantes of the lateral plantar artery during walking may act as a prime to the calf pump mechanism and so increase its efficiency. The purpose of the present study was to assess the effect of foot compression, when supine, on the velocity and volume of blood flowing in the popliteal and superficial femoral veins.

Methods

The subjects were five men and five women aged between 20 and 35 years. All were fit and healthy without symptoms or signs of venous disease. A total of 20 limbs were studied.

The foot was compressed with the A-V Impulse System (Novamedix, Andover, UK) shown in *Figure 1*. The device consists of an inflatable plastic pad, placed around the foot, which is connected to a pneumatic compressor and covered by a specially made inelastic slipper. The slipper directs the force produced when the pad is inflated inwards, squeezing the blood from the veins of the foot into the calf, thereby increasing the velocity of blood flow in the deep veins. The compressor delivers a square wave impulse of variable pressure, duration and frequency. The pressures, durations and frequencies studied were 50, 125 and 200 mmHg, 1 and 3 s, and 3 and 6 cycles per min respectively.

After the system had been applied to the foot, the subject lay supine on a couch for 5 min in a 10° foot-down position. Resting blood velocities (between inflations of the foot pad) and peak blood velocities (during foot pad inflation) in the popliteal and superficial femoral veins were measured for each combination of pressure, pulse duration and frequency of compression. The diameter of these vessels was also recorded. All measurements were made using an Acuson 128 (Acuson, Mountain View, California, USA) duplex scanner. The mean of four consecutive measurements of resting and peak velocity for each combination was used to calculate the change of venous flow in the following manner:

$$\text{Increase in velocity} = \text{peak velocity} - \text{resting velocity}$$

$$\text{Maximum increase in flow} = \text{cross-sectional area of vein} \times \text{increase in velocity}$$

Measurements of blood velocity and vein diameter made on one leg by one observer (B.A.) were compared with the same measurements taken in the opposite leg by another (K.S.); a good correlation was found between the measurements of each. Since the values of the increase in blood flow were found to be normally distributed, Student's *t* test, paired or unpaired as appropriate, was used for statistical analysis.

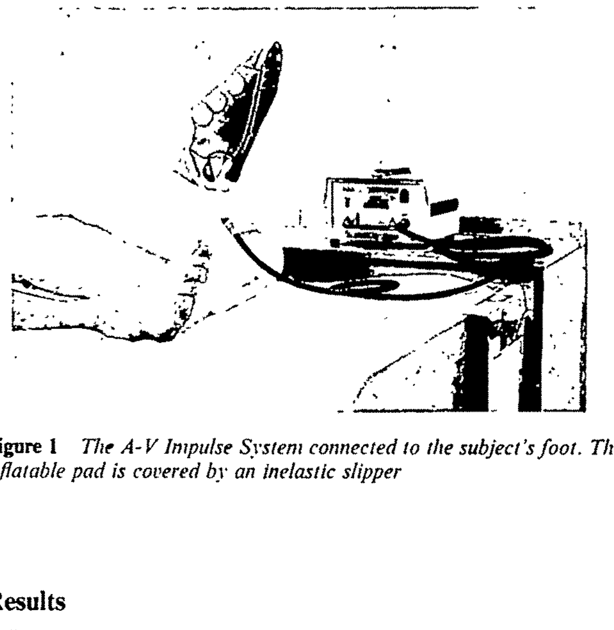

Figure 1 *The A-V Impulse System connected to the subject's foot. The inflatable pad is covered by an inelastic slipper*

Results

Effect of foot compression on maximum blood velocity

Initially, the effect of foot compression on the maximum velocity of venous blood in the popliteal and superficial femoral veins was investigated. There was a significant difference in the maximum velocity achieved, in both men and women, between pressures of 50 and 125 mmHg and between pressures of 125 and 200 mmHg in both the superficial femoral and popliteal veins ($P < 0{\cdot}001$). However, for a given pressure, the maximum velocity recorded in the popliteal vein was always greater than that in the superficial femoral vein. No significant difference was found in the maximum velocities of venous blood flow between men and women when similar pressures were used.

In the popliteal vein, for a compression of 50 mmHg the maximum velocity in men was 31·4 cm/s and in women 27·6 cm/s ($P < 0{\cdot}45$). For a compression of 125 mmHg the maximum velocity in men was 48·2 cm/s and in women 41·4 cm/s ($P < 0{\cdot}35$). At 200 mmHg this velocity was 53·5 cm/s in men and 47·9 cm/s in women ($P < 0{\cdot}46$). These findings and the results of blood velocity measured in the superficial femoral vein are summarized in *Table 1*.

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Table 1 *Effect of foot compression on the maximum velocity of blood in the superficial femoral and popliteal veins in men and women*

	Pressure (mmHg)					
	50		125		200	
	M	F	M	F	M	F
Superficial femoral vein	21·3(8·2)	18·3(8·1)	32·3(12·5)	28·0(12·1)	38·5(13·3)	33·3(13·1)
Popliteal vein	31·4(10·6)	27·6(11·3)	48·2(15·5)	41·4(16·4)	53·5(15·9)	47·9(17·3)

Values are mean(s.d.) expressed in cm/s

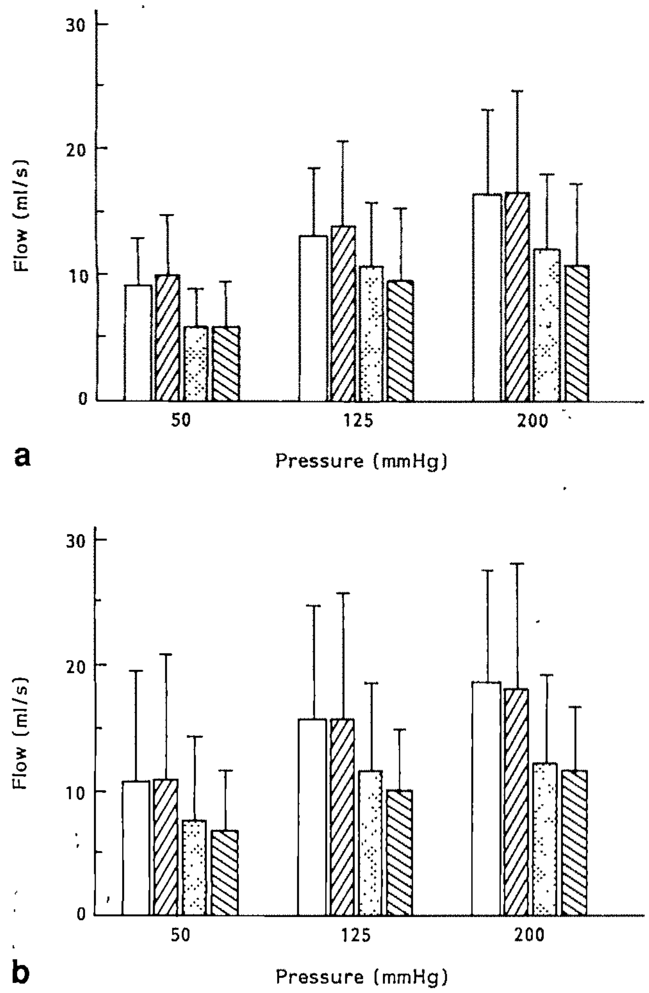

Figure 2 *Mean(s.d.) maximum increase in flow in* **a** *the superficial femoral and* **b** *the popliteal vein for all combinations of foot pressure. Values are for men and women combined (20 limbs) at 3 cycles per min (□, 1 s; ▨, 3 s) and 6 cycles per min (⬚, 1 s; ▩, 3 s)*

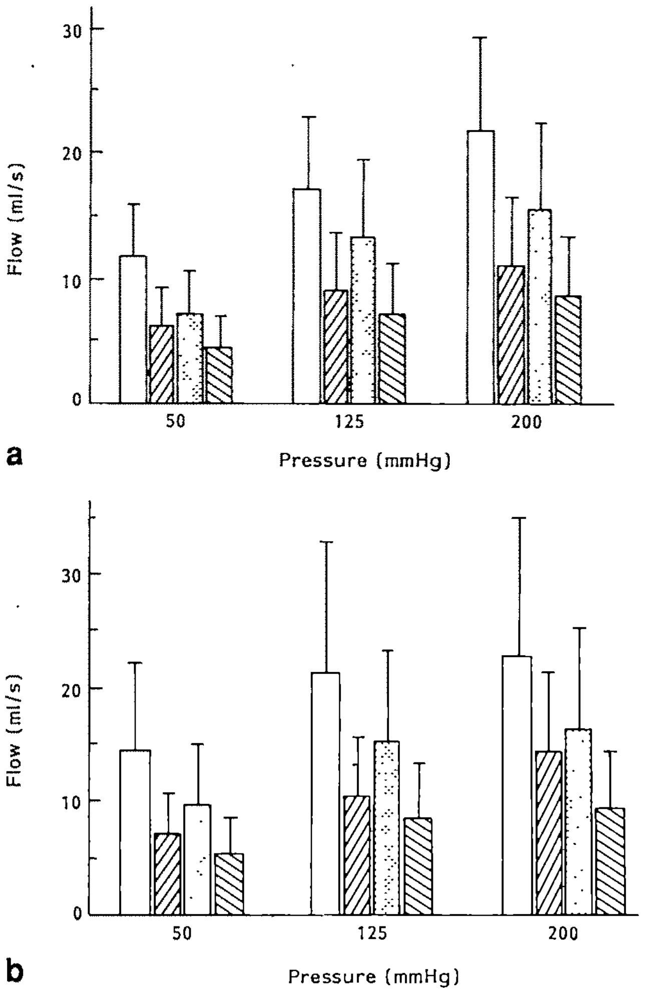

Figure 3 *Effect of sex on the mean(s.d.) maximum increase in flow in* **a** *the superficial femoral and* **b** *the popliteal vein for compression of 1-s duration only, there being no significant difference between compression lasting 1 or 3 s. Values are at 3 cycles per min for men (□) and women (▨) and at 6 cycles per min for men (⬚) and women (▩)*

Effect of foot compression on blood flow

The maximum increase in blood flow that occurred in the superficial femoral veins of men and women, for all the combinations of foot compression applied, are shown in *Figure 2a*. It can be seen that as the pressure in the compression system increased (from 50 to 200 mmHg), so too did the maximum increase in blood flow. Increasing the frequency of compression from 3 to 6 cycles per min reduced the maximum increase in flow. Increasing the duration of compression from 1 to 3 s had little or no effect on flow.

Similar changes were seen in the popliteal vein (*Figure 2b*) in both men and women. However, for all combinations of compression used, the increase in blood flow in women was significantly less than that in men (*Figure 3*).

The results shown in *Figures 2* and *3* are the mean maximum increases in flow for the various combinations of pressure, pulse duration and frequency. To determine how each of these compression variables affected the maximum increase in flow independently of the other two, it was necessary to analyse the data in a different way. For example, to compare the effect of a pulse duration of 1 s with that of 3 s a calculation was made of the mean value of the maximum increase in flow produced by a 1-s pulse duration in all subjects, at both sites and all combinations of pressure and frequency of compression, and this value compared with the similarly calculated maximum increase in flow for a 3-s pulse duration (*Table 2*).

Site variation and blood flow

There was no significant difference between the increase in blood flow that occurred in the popliteal and superficial femoral veins. The mean maximum increase in flow, for all combinations of pressure, pulse duration and frequency of foot compression, in the popliteal vein was 12·4 ml/s and in the superficial femoral vein 11·3 ml/s ($P > 0{\cdot}5$).

Table 2 *Effect of compression pressure, frequency and pulse duration on the maximum increase in blood flow, calculated from the pooled results of all limbs*

	Pressure (mmHg)			Frequency (cycles per min)		Duration (s)	
	50	125	200	3	6	1	3
Flow (ml/s)	9·0	13·4*	15·1	14·8	10·1†	12·6	12·3‡

* $P < 0{\cdot}001$ (125 *versus* 50 and 200 mmHg); † $P < 0{\cdot}001$ (3 *versus* 6 cycles per min); ‡ P not significant (1 *versus* 3 s); Student's paired t test

Sex variation and blood flow

There was a significant difference between the maximum increase in blood flow in men and women. The mean increase in flow in men was 14·2 ml/s, compared with 8·3 ml/s in women ($P < 0{\cdot}05$).

Variation of pressure and blood flow

There was a significant difference between the maximum increase in flow caused by each of the compression pressures studied. The mean maximum increase in flow with a compression of 50 mmHg was 9·0 ml/s, for 125 mmHg 13·4 ml/s and for 200 mmHg 15·1 ml/s ($P < 0{\cdot}001$). The sex differences previously noted were maintained, so that for any given compression men showed a significantly greater increase in peak flow than women. There was a linear relationship between the maximum flow in the axial vein and the degree of foot compression.

Variation of pulse duration and blood flow

No significant difference was found between the maximum increase in flow caused by pulse durations of 1 and 3 s. The overall mean increase in maximum flow for a 1-s pulse was 12·6 ml/s; for 3 s it was 12·3 ml/s ($P < 0{\cdot}1$).

Variation of frequency of compression and blood flow

The frequency of compression had a significant but inverse effect on blood flow for all combinations of pressure and pulse duration. The maximum increase in flow at 3 cycles per min was 14·8 ml/s, whereas a frequency of 6 cycles per min increased the flow by only 10·1 ml/s ($P < 0{\cdot}001$).

Discussion

In this study measurement was made of the maximum increase in blood flow rather than the total venous flow in a 1-min period because assessment of blood flow over a period of time requires repeated measurement of vein diameter, as it cannot be assumed that this diameter does not change when blood flow changes. A single measurement of blood velocity and vein diameter at the easily defined point of peak velocity was therefore made.

Maximum blood flows were different in men and women for all pressures, frequencies and durations of foot compression. Presumably this is related to the larger size of the male foot and its greater content of venous blood. Significant differences were found between the maximum velocity and flow generated by pressures of 50, 125 and 200 mmHg. However, when sex was considered, although there was a significant difference in maximum blood flow between men and women, no such difference in maximum velocities occurred. Until it is known whether increasing blood velocity or flow is the more important in the prevention of deep vein thrombosis (DVT), it is not possible to recommend different pressures of compression for men and women.

Altering the duration of compression from 1 to 3 s did not significantly affect the maximum increase in flow obtained for any given pressure or frequency. This is not surprising: once the foot has been emptied of blood, an event that takes about 1 s, no further blood can be expelled however long the compression lasts. Thus, for the purposes of prophylaxis of thrombosis, a variable duration of compression is of no value.

Increasing the frequency of compression significantly diminished the maximum flow achieved. The reduction in maximum flow at higher rates of compression is probably caused by the shorter time available for refilling the plantar veins, resulting in a smaller volume of blood being available to be pumped up the leg veins with each impulse. Doubling the frequency from 3 to 6 cycles per min did not, however, halve the peak flow; it fell by only 32 per cent. Thus over a 1-min period, 6 cycles per min would increase the flow velocity of a greater volume of blood than would a frequency of 3 cycles per min.

The Impulse System seems to be effective in the prevention of DVT. Bradley *et al.* (unpublished data) have shown that the incidence of venographically proven DVT following total hip replacement was reduced from 27 per cent in patients who received subcutaneous heparin (1000 units twice daily) and wore antiembolism stockings to 6·6 per cent in those treated with the Impulse System in addition. Fordyce and Ling[3] also showed a significant reduction in venographically proven DVT following total hip replacement, from 40 per cent in a control group to 5 per cent in a group treated by foot compression. Wilson *et al.*[4] have also demonstrated a reduction in both the incidence and extent of DVT following total knee replacement, from 69 to 50 per cent.

It may be that the compression system reduces the incidence of DVT by temporarily increasing the velocity of blood within the axial veins, causing the venous valves to open fully so expelling the relatively stagnant blood from within the valve sinuses, since it is here that DVT is thought to originate[5,6].

In this study the effects of foot compression have been quantified, showing how the variables of pressure, pulse duration and frequency affect blood flow in the axial veins. Only by performing a clinical trial would one be able to tell which of these parameters of foot compression is most efficacious in preventing DVT. Until such a trial is completed it is suggested that a compression of 250 mmHg lasting 1 s, repeated every 10 s (6 cycles per min), is appropriate.

References

1. Gardner AMN, Fox RH. The venous pump of the human foot – preliminary report. *Bristol Medicochirurgical Journal* 1983; **98**: 109–12.
2. Fox RH, Gardner AMN. Video-phlebography in the investigation of venous physiology and disease. *Phlebology* 1985; **19**: 68–70.
3. Fordyce MJF, Ling RSM. The prevention of deep vein thrombosis following total hip replacement by use of the A-V Impulse System. *J Bone Joint Surg [Br]* 1992; **74-B**: 45–9.
4. Wilson N, Das S, Kakkar V *et al.* Thromboembolic prophylaxis in total knee replacement, an evaluation of the AVI foot pump. *J Bone Joint Surg [Br]* 1992; **74-B**: 50–2.
5. Sevitt S, Gallagher N. Venous thrombosis and pulmonary embolism. A clinico-pathological study in injured and burned patients. *Br J Surg* 1961; **48**: 475–8.
6. Nicolaides AN, Kakkar VV, Field ES, Fish P. Venous stasis and deep vein thrombosis. *Br J Surg* 1972; **59**: 13–15.

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Case report

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Emergency aortic aneurysmectomy in a renal transplant recipient

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The increasing numbers of long-term survivors following renal transplantation will complicate the surgical management of subsequent diseases. The donor renal artery may be anastomosed to the recipient iliac artery, and any interruption of proximal blood supply for reconstructive arterial surgery will compromise graft function. This case report describes the successful repair of an abdominal aortic aneurysm (AAA) in a renal transplant recipient with preservation of renal blood supply using a temporary heparin-bonded axillofemoral shunt[1].

Case report

A 56-year-old man presented with a 1-h history of lower abdominal and back pain. Although having peripheral vasoconstriction he was haemodynamically stable with a blood pressure of 130/90 mmHg. A pulsatile mass in the abdomen was confirmed by computed tomography to be a ruptured 7·5-cm infrarenal AAA.

Some 24 years previously the patient had received a renal allograft, with vascular anastomoses to the right common iliac vessels (*Figure 1*), for the treatment of end-stage renal failure secondary to chronic glomerulonephritis. Long-term immunosuppression was maintained with prednisolone and azathioprine. The preoperative serum creatinine level was 137 μmol/l.

To preserve transplant function during the period of aortic cross-clamping, a heparin-bonded temporary right axillofemoral shunt (Gott aneurysm shunt; Sherwood Medical, St Louis, Missouri, USA) was inserted before laparotomy. The procedure took 20 min and the infrarenal aorta was cross-clamped 30 min after the beginning of the operation. A straight aortic graft was inserted, and then a left aortofemoral graft was anastomosed side to side to the common femoral artery to bypass an iliac occlusion. The shunt was then removed with closure of the arteriotomies, without a patch.

The patient's progress after operation was uneventful, although the serum creatinine level rose to 200 μmol/l in the first week. This returned to preoperative levels within 2 weeks and renal function remains normal 18 months after operation.

Discussion

The extended indications for renal transplantation and increasing success of immunosuppression have resulted in a greater number of patients with functioning renal transplants. Despite successful transplantation, atherosclerotic vascular disease secondary to chronic renal failure and long-term haemodialysis may remain progressive in a population that is now living to an older age.

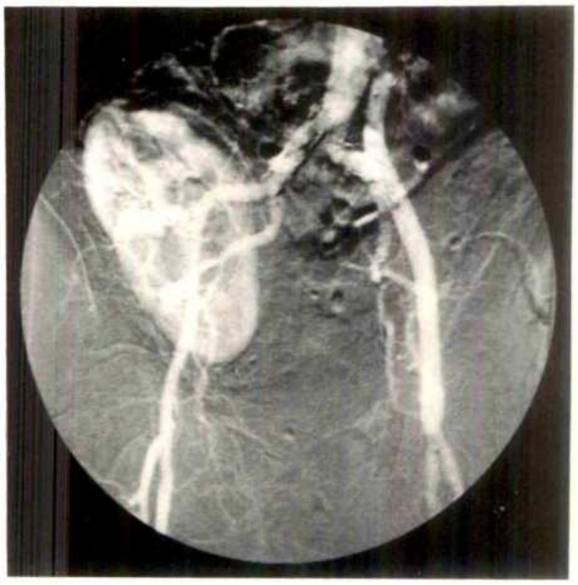

Figure 1 *Arteriogram showing the renal transplant anastomosed to native iliac vessels in the right iliac fossa*

Methods of preservation of graft function during the period of aortic cross-clamping for elective repair of AAAs include axillofemoral grafts or shunts, aortoiliac shunts[2], and femorofemoral bypass with a pump–oxygenator[3]. By contrast, there have been few reports of renal transplant recipients undergoing emergency surgery for ruptured aneurysms[4].

Lacombe uses no temporary vascularization of the transplanted kidney but transects the aorta between two clamps without opening the aneurysm sac[5]. The transplanted kidney is thus perfused at low pressure by retrograde flow from the inferior mesenteric, lumbar and iliac arteries while the proximal anastomosis is made, so limiting the period of warm ischaemia. This manoeuvre is not suitable for the ruptured aneurysm, where the kidney may have already suffered from a period of hypoperfusion and urgent revascularization is required. The Gott shunt can be inserted quickly, and the heparin bonding on the luminal surface obviates the need for systemic anticoagulation. These shunts should be made available in units carrying out vascular surgery and renal transplantation.

References

1. Gott VL, Furuse A. Antithrombogenic surfaces, classification and *in-vivo* evaluation. *Fed Proc* 1971; **30**: 1679–85.
2. O'Mara CS, Flinn WR, Bergan JJ, Yao JST. Use of a temporary shunt for renal transplant protection during aortic aneurysm repair. *Surgery* 1983; **94**: 512–15.
3. Campbell DA, Lorber MI, Arneson WA, Kirsch MM, Turcotte JG, Stanley JC. Renal transplant protection during abdominal aortic aneurysmectomy with a pump–oxygenator. *Surgery* 1981; **90**: 559–62.
4. Schwartz RA, Caracci BF, Peterson GJ. Successful repair of a ruptured abdominal aortic aneurysm in a renal transplant recipient. *Ann Vasc Surg* 1988; **2**: 189–92.
5. Lacombe M. Abdominal aortic aneurysmectomy in renal transplant patients. *Ann Surg* 1986; **203**: 62–8.

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Survey of minor surgery in general practice in the West of Scotland

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Since April 1990 certain minor surgical procedures have attracted an item-of-service payment for general practitioners (GPs). A postal survey was undertaken to obtain information about minor surgery in general practice in the West of Scotland and to find out whether further postgraduate education is required in this field. From a random stratified sample of 356 GPs, 311 (87·4 per cent) responded. Practitioners on health board minor surgery lists have increased minor surgery activity since April 1990; they prefer to perform the less technically demanding and time-consuming procedures on the eligible list. It is concluded that there is scope for increasing postgraduate education in minor surgery for GPs.

Until recently few general practitioners (GPs) in the UK regularly performed minor surgery[1]. However, in an attempt to transfer some of the workload in minor surgery from the hospital service into the community[2], this activity became an item-of-service payment for GPs from April 1990. The full impact of this change in remuneration on working practices in general practice is not yet clear.

This study aimed to obtain information about minor surgery in the West of Scotland and to assess the need for postgraduate education relating to this activity.

Methods

A list of general practices and GPs was obtained from each of the six health boards in the West of Scotland. A total of 610 practices and 1830 practitioners were counted from the health board lists. The GPs were stratified by sex, health board area and number of partners, and a sample of 400 selected at random to reflect these factors. However, the list was slightly out of date and a number of GPs selected had retired or resigned. A 26-item questionnaire was devised requesting details about the GP, the practice, participation in minor surgery and arrangements for this activity. This was posted to GPs in March 1991 with a stamped addressed envelope for return. If no reply was obtained within 3 weeks a reminder was sent.

Statistical analysis was by χ^2 test.

Results

Forty-one GPs were excluded from the original list of 400 because of resignation, sickness, retirement, death or maternity leave and three questionnaires were returned marked 'not known at address'. Of the remaining 356 questionnaires, 311 (87·4 per cent) were completed correctly. The characteristics of the respondents are shown in *Table 1*. Of the respondents, 296 were full-time, 188 vocationally trained and 88 in training practices. A total of 188 had had previous experience of minor surgery beyond preregistration house officer level and that obtained in general practice; 154 gained this experience in accident and emergency posts, 31 in surgical positions up to and including consultant surgeon level, nine overseas, eight in dermatology posts and four during military service. This was an open question allowing more than one option.

A total of 194 GPs were on a health board minor surgery list; of the 117 not on such a list, 55 still performed minor surgery. More than one reason for not being on the list was possible and those given were: not eligible (62), too busy (62), not interested (50), not cost effective (46) and 'other' (19). The other reasons included unsuitable premises, a partner already on the list, physical disability and medicolegal worries. Some practitioners were awaiting the outcome of an application to join the list and some thought they were unable to apply because they were not prepared to perform all of the procedures on it. The characteristics of GPs who were on a minor surgery list compared with those who were not are shown in *Table 2*.

Table 1 *Characteristics of 311 respondents to minor surgery questionnaire*

Sex ratio (M:F)	228:83
Age (years)	
26–30	20
31–35	71
36–40	50
41–45	54
46–50	33
51–55	38
56–60	29
61–65	15
>65	1
No. of partners in practice	
1	71
2	61
3	65
4	50
5	34
6	18
7	5
8	4
>8	3
No. of patients per partner	
<500	3
501–1000	18
1001–1500	92
1501–2000	140
2001–2500	47
2501–3000	9
>3000	2
Health board area	
Argyll and Clyde	61
Ayrshire and Arran	33
Dumfries and Galloway	20
Forth Valley	31
Lanark	47
Greater Glasgow	119
Type of practice*	
Urban	190
Rural	53
Urban and rural	28
Semirural	25
Island	12

*Three respondents did not complete this section

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Table 2 *Characteristics of general practitioners on and not on health board minor surgery lists*

	On list ($n = 194$)	Not on list ($n = 117$)	P*
Sex ratio (M:F)	153:41	75:42	
Age <45 years	130	64	<0·05
Vocationally trained	131	57	<0·001
Experienced in minor surgery	140	48	<0·001
In training practice	68	20	<0·001
In urban practice	108	82	<0·05
In practice with ⩾5 partners	50	14	<0·005

*χ^2 test

Table 3 *Number of general practitioners on minor surgery lists performing estimated number of procedures per quarter before and after April 1990*

No. of procedures	Before April 1990	After April 1990
0	16	7
1–5	52	19
6–10	49	46
11–15	28	40
16–20	22	36
21–30	11	20
31–40	5	9
41–50	0	4
>50	9	11
Total*	192	192

*Two respondents did not complete this section

Table 4 *Individual procedures performed by general practitioners per quarter between April 1990 and March 1991*

	No. of practitioners performing procedure	No. of procedures performed per practitioner	Total no. of procedures performed
Periarticular injection	144	0–20	525
Abscess incision	139	0–12	301
Sebaceous cyst excision	92	0–10	213
Curette, cautery and cryocautery of warts or verrucas	90	0–98	1045
Removal of foreign bodies	89	0–8	130
Intra-articular injection	81	0–36	448
Excision of skin lesions for histology	80	0–18	217
Removal of toenails (partial and complete)	74	0–13	221
Cyst incision	57	0–6	98
Cyst aspiration	56	0–7	99
Bursa aspiration	56	0–4	76
Joint aspiration	54	0–15	87
Excision of warts	54	0–10	140
Excision of intradermal naevi, papilloma, dermatofibroma and similar conditions	54	0–20	139
Curette, cautery and cryocautery of other lesions	41	0–34	125
Excision of lipoma	28	0–8	62
Thrombosed pile incision	27	0–2	32
Hydrocele aspiration	25	0–3	31
Nasal cautery	21	0–13	65
Varicose vein injection	6	0–2	10
Haemorrhoid injection	2	0–3	4

The 194 respondents on a minor surgery list were asked to estimate the number of procedures performed in an average quarter before April 1990 and in an average quarter after that date. There was a shift towards increasing the number of procedures after April 1990, as shown in *Table 3*. The individual procedures the 194 practitioners performed are shown in *Table 4*. The mean and median are not included; these measures were unhelpful because the majority of GPs in the study performed only a small number of procedures. In an open question, 50 of the 194 respondents said that injection of varicose veins should not be included on the list of eligible procedures for reimbursement; 41 felt similarly about haemorrhoid injection. It was felt by 46 that suture of lacerations should be included on the list.

Minor surgery was performed opportunistically by 156 GPs, 74 arranged a regular session, ten arranged a nurse-run clinic, four had hospital-run clinics, three had special appointments and three had special wart clinics; more than one option was possible for this question. Ninety-two had access to cryotherapy. Ninety-four used an autoclave for sterilizing instruments, 43 a local hospital or central sterile supplies department, 20 used disposable instruments, 14 employed a water boiler, nine used chemical methods of sterilization and 26 did not answer this question; this was an open question and more than one method was used by some practitioners. Removed specimens were sent for histological examination by 165 GPs; the majority of those who did not had yet to remove any suitable specimens. A total of 169 obtained verbal consent for procedures, 15 written consent, two both verbal and written consent, six no consent and two did not answer this question.

Financial remuneration for minor surgery was thought adequate by 107 GPs, inadequate by 79 and eight did not answer this question. Fifty-nine estimated that they made a profit of more than £100 per partner per quarter from minor surgery, 39 less than £100, 30 no profit and seven a net loss; the remainder did not know or did not answer this question.

Discussion

The response rate of 87·4 per cent in this audit compares favourably with that of other postal surveys and reflects the high level of cooperation between GPs in the West of Scotland and the University of Glasgow. The sample is representative of practitioners in the region for sex, age, number of partners and number of patients per partner. Before April 1990 the amount of minor surgery being performed in general practice was declining[3] but the survey suggests that, at least for those GPs on their health board minor surgery list, in this region this trend has been reversed. However, as in any retrospective study based on the individual's recall, there is an immediate source of bias. Although it might have been possible to validate the numbers of procedures for which a claim was made by GPs from the health boards after April 1990, this would not account for any procedures performed over and above the 15 per quarter that can be reimbursed. In addition, there is no method for checking the number of procedures performed before April 1990.

Few GPs in this study performed the more difficult procedures, such as injection of varicose veins and haemorrhoids, and this confirms the findings of other workers[4]. This may be because the majority lack confidence in performing such procedures because of inadequate training and experience, both in diagnosis and surgical technique. Alternatively, practitioners may believe these are not cost effective when the payment is the same as for ablating warts by cryotherapy, for example. A substantial minority felt that injection of varicose veins and haemorrhoids should not be included in the list of eligible procedures, but this could deter those GPs who feel qualified and willing to perform them. Perhaps a two-tier system of payment would be more appropriate than the current standard fee for every procedure; simple procedures would be paid at a lower level than more difficult ones. Other practitioners felt that suturing of lacerations should be included on the list of eligible procedures, suggesting the possibility that the minor surgery list of procedures is too prescriptive.

In this study most minor surgery was arranged opportunistically, confirming Castle's finding[4]. It could be argued that a separate session with appropriate back-up should be a longer term aim. The high percentage of GPs who sent removed specimens for histological analysis and used suitable methods for sterilizing instruments was reassuring[5]. Less reassuring was the finding that 87 per cent obtained only verbal consent for performing minor surgical procedures. This is a source of medicolegal concern and may require the issuing of specific guidelines.

Patients have been shown to be highly satisfied by general practice minor surgery, which costs considerably less than the same treatment in hospital[6]. However, to increase services to patients and reduce hospital waiting lists, most GPs will probably need to do minor surgery[7]. In this study just over 60 per cent of the practitioners were on their health board minor surgery list and, although almost half of those not on a list were performing minor surgery, it should be possible to encourage even more to become active in minor surgery. Practitioners not on a list gave a number of reasons for this; however, over half said they were not eligible. In addition, 40 per cent of the original study group had no relevant experience above preregistration house officer level and that obtained in general practice. It would seem appropriate, therefore, to improve opportunities for GPs to obtain the necessary experience to be accepted for the minor surgery list. Previous workers have shown that preregistration house officer experience is inadequate training for all the procedures on the minor surgery list[7]. There is scope for increasing teaching in minor surgery at this level, particularly because about half of all house officers become GPs.

The alternative is to develop skills in minor surgery as a vocational trainee, many of whom undertake accident and emergency and surgical jobs that often provide the relevant experience. Indeed, as demonstrated by this study, accident and emergency is the main source of experience in minor surgery for most GPs. Perhaps it should be ensured that the content of these posts addresses the requirements of the minor surgery list for general practice trainees. However, this would not help those who are currently working as GPs and are not eligible for their health board lists. This study has identified a need for postgraduate courses in minor surgery in the West of Scotland. Guidelines on the content of such courses have been produced by the General Medical Services Committee and The Royal College of Surgeons of England, The Royal College of Surgeons of Edinburgh and the Joint Committee on Postgraduate Training for General Practice[8]. Further collaboration on suitable training for minor surgery has also been proposed between The Royal College of General Practitioners and The Royal College of Surgeons of England (personal communication, Royal College of General Practitioners).

Acknowledgements

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References

1. Hall DW. A review of minor surgery in general practice in the United Kingdom. *Fam Pract* 1987; **4**: 322–9.
2. *General Practice and the National Health Service. The 1990 Contract.* Health Departments of Great Britain. London: HMSO, 1989.
3. Humby M. Minor surgery. *Practitioner* 1988; **232**: 227.
4. Castle C. Minor surgical procedures performed by general practitioners. *Br J Gen Pract* 1990; **40**: 430 (Letter).
5. Morgan DR, Lamont TJ, Dawson JD, Both C. Decontamination of instruments and control of cross infection in general practice. *BMJ* 1990; **330**: 1379–80.
6. Milne R. Minor surgery in general practice. *Br J Gen Pract* 1990; **40**: 175–7.
7. Pringle M, Hasler J, De Marco P. Training for minor surgery in general practice during pre-registration surgical posts. *BMJ* 1991; **302**: 830–2.
8. General Medical Services Committee and The Royal College of General Practitioners in collaboration with The Royal College of Surgeons of England, The Royal College of Surgeons of Edinburgh and the Joint Committee on Postgraduate Training for General Practice. *Minor Surgery in General Practice.* December 1991.

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Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery

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Expression of class II major histocompatibility complex (MHC) on monocytes is a prerequisite for effective antigen presentation and processing, an important component of the immune response to infection. It has been reported that the level of monocyte class II expression may identify patients who go on to develop infective complications following trauma. In the present study, flow cytometry was used to measure MHC class II (human leucocyte antigen (HLA)-DR) expression on circulating monocytes and T cells in 36 patients undergoing elective major resectional surgery, of whom 12 developed septic complications. The percentage of HLA-DR positive monocytes fell significantly on the first day after operation in both groups ($P < 0{\cdot}0001$) but was significantly higher in those without than in those with sepsis on days 1, 3 and 5 ($P < 0{\cdot}05$). In contrast, the level of T cell HLA-DR expression rose significantly on the first day after operation ($P < 0{\cdot}05$) in patients without sepsis to a level higher than in those who developed infection ($P < 0{\cdot}05$). These findings have important implications, as predictive biological elements and for biological response modification, in patients at risk of developing sepsis after surgery.

Sepsis remains the single most important cause of morbidity and mortality in all branches of surgery. Current surgical practice and intensive care treatment have enabled progressively more complex procedures to be undertaken in older and more debilitated patients than previously possible[1]. However, despite the introduction of new generations of antibiotics, the overall incidence of sepsis after elective surgery[2] remains in the region of 5–10 per cent; this has not changed over the past decade[3]. It has been suggested that such sepsis may be a reflection of post-traumatic changes in leucocyte function[4–6]. Many facets of immune function have been shown to be impaired following major surgery; such data have been acquired using a range of techniques. At least half of the patients who undergo gastrointestinal surgery become anergic as assessed by delayed hypersensitivity skin testing and this anergy is associated with an increased risk of postoperative sepsis[7]. Similarly, defects in neutrophil chemotaxis, phagocytosis, lysosomal enzyme content and respiratory burst have all been identified after operation[8]. Major surgery has also been shown to reduce the ratio of T helper to T suppressor cells and to reduce the number of circulating natural killer cells[4]. *In vitro* studies have revealed defective monocyte interleukin (IL) 1 secretion and increased prostaglandin (PG) E_2 secretion after major injury[9], reversing the normal balance of stimulatory macrophage secretions for T cell activation.

The expression of major histocompatibility complex (MHC) class II is pivotal in the specific immune response to antigen. The initial event in antigen processing is the uptake of antigen by the macrophage into cellular lysosomes, where short polypeptide sequences are generated and combined with newly synthesized MHC class II antigen and expressed on the cell surface[10]. T helper cells will recognize only foreign antigens presented in conjunction with self MHC class II antigen[11,12]. Because measurements of the level of MHC class II expression may identify patients who go on to develop infective complications after trauma[13] and because of the central importance of MHC expression in the immune response to infection, levels of MHC class II antigen expression in peripheral circulating T cells and monocytes in patients undergoing major elective surgery were studied; the aim was to determine whether such measurements might predict the development of septic complications.

Patients and methods

The study was conducted in 36 consecutive patients undergoing elective major or complex major surgical procedures (*Table 1*); clinical profiles were recorded (*Table 2*). All patients received preoperative antibiotic prophylaxis with metronidazole and a cephalosporin, which was continued for 48 h after surgery.

Venous blood (4 ml) was collected from the patients between 08.00 and 09.00 hours before surgery and on days 1, 3, 5, 7 and 10 afterwards. Blood was collected in polypropylene tubes containing 1 ml chilled acid citrate dextrose (NIH formula A; Travenol Laboratories, Thetford, UK) as anticoagulant and sodium azide at a final concentration of

Table 1 *Type of procedure for 36 consecutive patients undergoing elective surgery*

	No.
Left or right hemicolectomy	7
Total colectomy	5
Anterior resection	2
Abdominoperineal resection of rectum	1
Small bowel resection	6
Total oesophagectomy	4
Pancreatoduodenectomy and colectomy	2
Hepatic resection	1
Total gastrectomy	3
Miscellaneous retroperitoneal resectional surgery	5
Total	36

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Table 2 *Clinical profiles of 36 consecutive patients undergoing elective surgery*

	Patients with no complications ($n = 24$)	Patients developing infection ($n = 12$)
Age (years)*	66 (31–84)	64 (31–79)
Sex ratio (M:F)	14:10	9:3
APACHE II score*	2·5 (0–7)	2·5 (0–8)
Malignancy (%)	60	67
Albumin level (g/l)*	41 (31–46)	39 (36–40)
Blood transfusion (units)*	0 (0–2)	0 (0–7)
Patients receiving transfusion	5	6

*Values are median (range)

0·01 per cent and placed immediately on ice. A 100-μl aliquot of this anticoagulated blood was then added to 10-μl aliquots of phycoerythrin-conjugated anti-human leucocyte antigen (HLA)-DR monoclonal antibody, with either fluorescein isothiocyanate-conjugated anti-cluster differentiation (CD)3 monoclonal antibody or anti-CD14 monoclonal antibody and incubated for 30 min, for assessment of T cell and monocyte HLA-DR expression respectively (monoclonal antibodies from Becton–Dickinson, Cowley, UK).

After incubation with the antibodies, erythrocytes were lysed using fluorescence-activated cell sorter lysing solution (Becton–Dickinson); these procedures were carried out in lipopolysaccharide-free polypropylene plastics at 4°C in the dark. The samples were then washed twice in modified Dulbecco's phosphate-buffered saline without calcium or magnesium, but with added ethylenediamine tetra-acetic acid, bovine serum albumin and sodium azide. All samples were run within 4 h of venepuncture through a FACScan flow cytometer using Consort 30 acquisition software and Lysis analysis software (Beckton–Dickinson).

Analysis of HLA-DR expression in lymphocytes and monocytes was conducted by gating on the leucocyte subpopulation of interest by virtue of its light-scattering properties. The simultaneous red and green fluorescence of this region was then plotted on a two-dimensional scattergram. The degree of red fluorescence of the CD3- or CD14-positive band was then measured and expressed either as the percentage positive (those cells that fluoresce brighter than a marker set up on a control monocyte or lymphocyte population stained with an irrelevant isotypic matched antibody) or a mean channel fluorescence, an indicator of the mean number of HLA-DR antigen complexes expressed per cell. This dual-colour technique thereby excluded any cells that may have fallen within the given light-scattering regions.

Lymphocyte and monocyte HLA-DR expression between patient groups was compared using two-way analysis of variance (ANOVA), with either the percentage positive figure or the mean channel fluorescence as the dependent variable. If ANOVA demonstrated significant intergroup differences, Student's unpaired t tests were performed at individual time points.

Patients were defined as having an infective complication if a systemic response to infection was clinically evident (two or more of the following: peripheral white cell count $< 2 \times 10^9$/l or $> 15 \times 10^9$/l; temperature > 38°C; twofold increase in serum alkaline phosphatase level; prothrombin time > 18 s; bilirubin level > 20 μmol/l; hypotension, i.e. systolic blood pressure < 100 mmHg for ≥ 2 h; and tachycardia > 100 per min for ≥ 2 h), along with clinical evidence of an infection site.

A χ^2 test was performed on discrete variables. Results were considered different at $P < 0{\cdot}05$; data are expressed as mean(s.e.m.).

Results

Of the 36 patients undergoing the elective procedures listed, 12 developed an infective complication. Pulmonary infection, wound infection and intraperitoneal abscess occurred with equal incidence; there was no postoperative death in either group and at no time did any patient have a positive blood culture. The development of infection defined the patient subgroups (with sepsis and uncomplicated) for the purpose of retrospective analysis of preoperative clinical profile and postoperative changes in HLA-DR expression of monocytes and T cells. Before operation the two subgroups were not significantly different with regard to age, sex ratio, APACHE II score, incidence of neoplasia and serum albumin level, or in number of units of blood transfused in the perioperative period. Two patients were receiving corticosteroid treatment before surgery and two were non-insulin dependent diabetics receiving medication; all four had an uncomplicated postoperative course.

HLA-DR expression on CD14$^+$ mononuclear cells

Within 24 h of general anaesthesia and major surgery, there was a significant reduction in the percentage of circulating monocytes expressing the HLA-DR antigen in both the uncomplicated group and the patients with sepsis (mean(s.e.m.) percentage before operation *versus* 1 day after surgery 87·4(2·2) *versus* 63·7(4·5) and 83·9(3·6) *versus* 48·1(5·1) for the uncomplicated group and patients with sepsis respectively, $P < 0{\cdot}0001$). The mean(s.e.m.) percentage of monocytes expressing the HLA-DR antigen returned to the preoperative level by day 5 after surgery in the uncomplicated group (78·5(4·5), P not significant) and by day 7 in those who suffered infections (69·2(6·7), P not significant). The percentage of monocytes positive for the HLA-DR antigen was lower in patients who developed an infective complication than in those with an uncomplicated postoperative course for the entire postoperative period ($P < 0{\cdot}0001$, ANOVA), reaching statistical significance on days 1, 3 and 5 (respective mean(s.e.m.) percentages for uncomplicated *versus* sepsis: 63·7(4·5) *versus* 48·1(5·1), $P < 0{\cdot}04$; 69·8(4·7) *versus* 56·2(3·8), $P < 0{\cdot}05$; and 78·5(4·5) *versus* 53·1(5·2), $P < 0{\cdot}005$) (*Figure 1*).

Likewise, the level of HLA-DR antigen expression per monocyte, expressed as mean(s.e.m.) channel fluorescence, in both the patients with sepsis and the uncomplicated group fell on the first day after operation (82·4(11·1) *versus* 27·7(4·3), $P < 0{\cdot}001$ and 69·5(12·1) *versus* 20·1(3·6), $P < 0{\cdot}0001$, respectively). This parameter returned to preoperative levels by day 10 after operation in both groups (68·5(11·1) and 51·1(13·3), uncomplicated and group with sepsis respectively). Again, before operation and for the entire period after operation the mean(s.e.m.) density of the HLA-DR antigen per monocyte was greater in the uncomplicated group of patients than in those with sepsis ($P < 0{\cdot}004$, ANOVA), reaching statistical significance on day 3 (36·9(5·1) *versus* 21·9(3·2), $P < 0{\cdot}05$) (*Figure 2*). At no stage in the postoperative period did a binomial pattern develop in the frequency histograms of monocyte HLA-DR expression, which simply shifted to the left. Thus no subpopulation of cells expressing low amounts of HLA-DR appeared that reduced the percentage of monocytes expressing high levels.

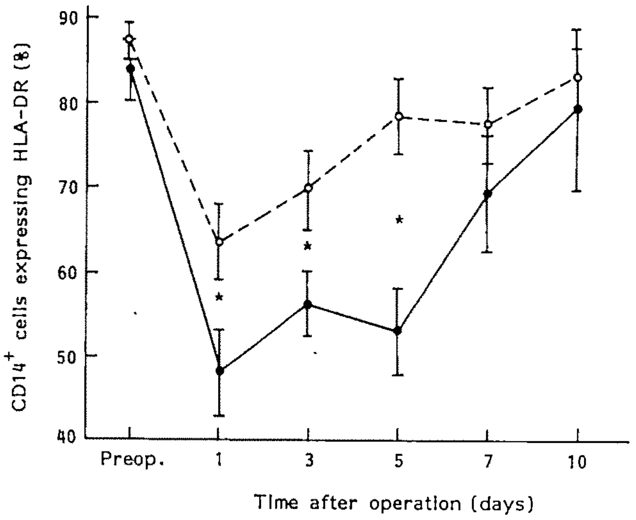

Figure 1 *Postoperative change in percentage of CD14$^+$ mononuclear cells positive for the human leucocyte antigen (HLA)-DR antigen for patients with no complications* (○) *and with sepsis* (●). *Values are mean(s.e.m.).* $P < 0{\cdot}0001$ *between groups (two-way ANOVA);* *$P < 0{\cdot}05$ *(Student's unpaired* t *test)*

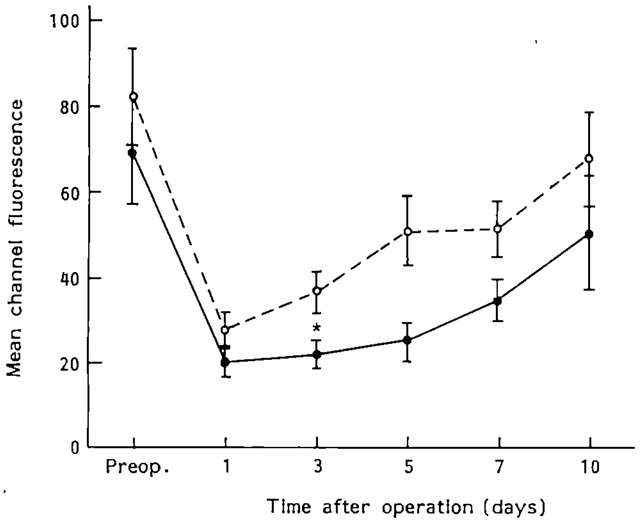

Figure 2 *Postoperative change in human leucocyte antigen (HLA)-DR antigen expression in CD14$^+$ mononuclear cells for patients with no complications* (o) *and with sepsis* (●). *Values are mean(s.e.m.).* $P < 0·005$ *between groups (two-way ANOVA);* $^*P < 0·05$ *(Student's unpaired* t *test)*

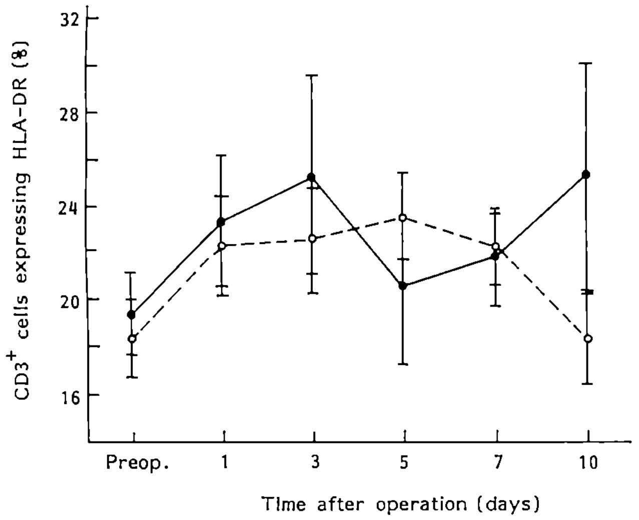

Figure 3 *Postoperative change in percentage of CD3$^+$ mononuclear cells positive for the human leucocyte antigen (HLA)-DR antigen for patients with no complications* (o) *and with sepsis* (●). *Values are mean(s.e.m.).* $P = 0·5$ *between groups (two-way ANOVA)*

HLA-DR expression on CD3$^+$ mononuclear cells

There were no statistically significant intergroup differences in the postoperative changes that occurred in the percentage of circulating T cells expressing the HLA-DR antigen (*Figure 3*). However, in patients who had an uncomplicated postoperative course there was a significant rise in the T cell mean(s.e.m.) channel fluorescence for the HLA-DR antigen from before operation to day 1 (2·3(0·2) *versus* 3·1(0·3), $P < 0·05$). This was significantly higher than in patients who developed an infective complication (3·1(0·3) *versus* 2·2(0·2), $P < 0·05$) (*Figure 4*). Again, both before operation and throughout the postoperative period the mean density of the HLA-DR antigen per T lymphocyte was greater in the uncomplicated group than in those patients who developed sepsis ($P < 0·002$, ANOVA).

The incidence of leucocytosis and febrile episodes was similar in the early postoperative period in both groups of patients. In the group with sepsis, 85 per cent of positive bacterial cultures were obtained in the late postoperative period (arbitrarily defined as beyond the fifth day after surgery).

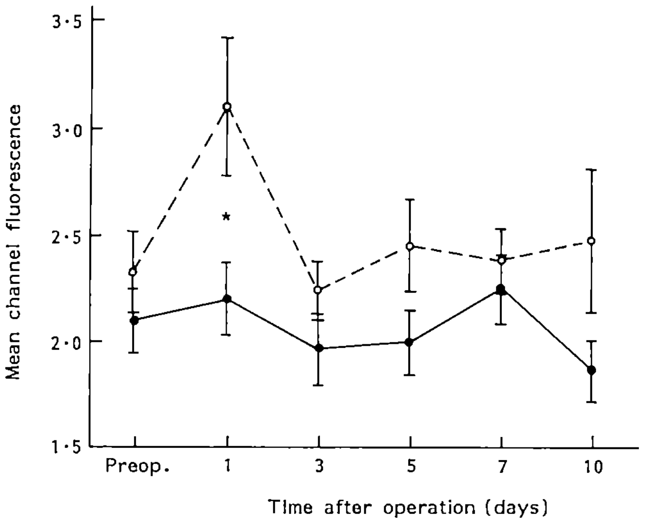

Figure 4 *Postoperative change in human leucocyte antigen (HLA)-DR antigen expression in CD3$^+$ mononuclear cells for patients with no complications* (o) *and with sepsis* (●). *Values are mean(s.e.m.).* $P < 0·002$ *between groups (two-way ANOVA);* $^*P < 0·05$ *(Student's unpaired* t *test)*

Discussion

In the present study the percentage of monocytes positive for the HLA-DR antigen was similar to those previously described by others[14]. A consistent theme throughout the present data was that MHC class II expression was greater in the uncomplicated group than in the group with sepsis before operation, and this difference was maintained and amplified after operation. Although the preoperative differences were not statistically significant, it is an interesting feature, because inherited traits towards high or low levels of expression have been observed previously[15] and may indicate the presence of a genetic component to the modifications of immune function induced by injury.

A number of studies have documented a reduction in the percentage of circulating HLA-DR positive monocytes following major trauma[13], burn injuries[16] and laparotomy in mice[17] and in humans[15]. However, in addition to confirming the results of these previous studies, which did not discriminate uncomplicated from septic outcomes, the present study has shown that both the percentage of monocytes positive for the HLA-DR antigen and the mean antigen density followed a parallel postoperative pattern. This suggests that there is a downregulation of HLA-DR at the cellular level rather than the percentage of DR-positive monocytes being reduced by an influx of immature monocytes as suggested by other workers[15]. In support of this is that, when analysing the frequency histograms of monocyte HLA-DR expression, no binomial pattern evolved in the postoperative period, i.e. no obvious subpopulation of low-level expressers emerged, merely a shift in the histogram mode to the left.

It is proposed that, as after trauma, the reduction in HLA-DR expression following surgery is associated with postoperative infection. Although the exact mechanism for this downregulation is unknown, experimental data are accumulating that may provide several possible explanations. Shock and trauma have emerged as inter-related entities that have detrimental effects on components of the immune system. Experimentally, simple haemorrhage without significant tissue trauma causes major modifications in the immune system[17] despite adequate volume replacement, and both MHC class II expression and the antigen-presenting potential of monocytes are profoundly reduced[18]. In the elective surgical setting, intraoperative haemorrhage is likely to be managed with blood or blood product transfusions, and these themselves are known to be immunosuppressive[19]. A number of studies report that following haemorrhage there is release of endotoxin[20] that may further confuse the interpretation of immunological measurements in these patients. In the present study the incidence of perioperative blood transfusion was similar in both groups and, although transfusion may contribute to the alteration of monocyte HLA-DR expression, it is unlikely to be a major influential factor in the final outcome.

Anaesthesia itself has been reported to alter host defences in normal individuals and this may be caused by a direct pharmacological effect or secondary to a state of relative peroperative hypotension that may be unavoidable. It has been claimed that the immunosuppressive effects of anaesthesia may be of benefit, insofar as the administration of an anaesthetic attenuates the secretion of tumour necrosis factor (TNF) and its possible deleterious effects in response to endotoxin release[21].

Within the monocyte–T cell axis a number of alterations in cytokine secretion have been described following surgery and haemorrhage. The macrophage exerts its stimulatory and regulatory functions within a specific immune response via the secretion of IL-1 and PGE$_2$. After trauma and surgery the macrophage secretion of PGE$_2$ is significantly raised and that of IL-1 significantly reduced[9]. IL-1 is required for normal macrophage–T cell interaction, this interaction being impaired by PGE$_2$. Failure of the appropriate macrophage–monocyte secretion may be one reason why there was a failure of T cell activation as assessed by T cell HLA-DR expression in the present patients who developed infective complications. Diminished interferon (IFN) γ production after trauma has been described[9]; it has been suggested that the administration of exogenous IFN-γ may be effective in reducing the incidence of infection in trauma victims[22] and that this improved outcome is mediated by increased levels of monocyte HLA-DR expression in severely injured patients[23]. The same investigative group is now evaluating the effects of IFN-γ treatment in trauma victims in a prospective randomized controlled trial[24]. Similarly, granulocyte–macrophage colony-stimulating factor is known to increase monocyte HLA-DR expression and antigen-presentation capacity[25,26], the circulating levels of this cytokine being depressed in burn victims who develop infective complications[27].

The endocrine response to surgery is one of raised cortisol secretion that even in the physiological range can suppress components of the immune system. Dexamethasone has been shown to downregulate IFN-γ-induced monocyte MHC class II expression[28], but no correlation between the level of cortisol and degree of postoperative immunosuppression has yet been shown[29].

The MHC also has a number of regulatory functions mediated by its monomorphic determinants. The density of class II molecules on the monocyte cell surface can alter the degree of immune responsiveness of an individual, in particular the degree of T cell responsiveness[30,31]. In the patients with sepsis in the present study it may be that monocyte class II expression fell below a critical level, such that there was a failure of T cell activation in these patients as shown by increased HLA-DR expression in CD3$^+$ cells in the group with no complications but not those with sepsis. In addition to exerting a regulatory role over T cell activation, the monocyte class II antigen also regulates the monocyte secretion of IL-1 and TNF. The lipopolysaccharide-induced secretion of TNF and IL-1 can be reduced in a dose-dependent manner by prior incubation with monoclonal antibodies to the DR and DQ determinants. The secretion of these cytokines shows a degree of polymorphic variation; in general, heterozygotes at the HLA-DR locus are 'higher' secretors than homozygotes[32].

Although the mechanism by which the postoperative reduction of HLA-DR expression in the monocyte occurs is unknown, its immunological consequences may be mediated through multiple pathways. The importance of this is exemplified in the clinical outcome of the present patients, where the greater fall in monocyte HLA-DR expression and delayed return to normal levels was observed in those who subsequently developed infective complications. In these patients there was associated failure of T cell activation that may have contributed to the development of infective complications.

This perturbation of MHC expression on monocytes and T cells occurs as early as the first 24 h after elective surgery in patients who are destined to develop infective complications, before any clinical manifestations are apparent. The measurement of HLA-DR expression may serve to predict this complication and also as a target for future modifications by biological agents.

Acknowledgements

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References

1. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med* 1985; **13**: 818–29.
2. Polk HC Jr. Non-specific host defence stimulation in the reduction of surgical infection in man. *Br J Surg* 1987; **74**: 969–70.
3. Fife D, Kraus J. Infection as a contributory cause of death in patients hospitalized for motor vehicle trauma. *Am J Surg* 1988; **155**: 278–83.
4. Lennard TWJ, Shenton BK, Borzotta A *et al.* The influence of surgical operations on components of the human immune system. *Br J Surg* 1985; **72**: 771–6.
5. Faist E, Kupper TS, Baker CC, Chaudry IH, Dwyer J, Baue AE. Depression of cellular immunity after major injury. *Arch Surg* 1986; **121**: 1000–5.
6. Hamid J, Bancewicz J, Brown R, Ward C, Irving MH, Ford WL. The significance of changes in blood lymphocyte populations following surgical operations. *Clin Exp Immunol* 1984; **56**: 49–57.
7. Meakins JL, Pietsch JB, Bubenick O *et al.* Delayed hypersensitivity: indicator of acquired failure of host defenses in sepsis and trauma. *Ann Surg* 1977; **186**: 241–50.
8. Utoh J, Yamamoto T, Utsunomiya T, Kambara T, Goto H, Myauchi T. Effect of surgery on neutrophil functions, superoxide and leukotriene production. *Br J Surg* 1988; **75**: 682–5.
9. Faist E, Mewes A, Strasser T *et al.* Alteration of monocyte function following major injury. *Arch Surg* 1988; **123**: 287–92.
10. Hackett CJ, Yewdwell JW, Benninck JR, Wysocka M. Class II MHC-restricted T cell determinants processed from either endosomes or the cytosol show similar requirements for host protein transport but different kinetics of presentation. *J Immunol* 1991; **146**: 2944–51.
11. Creswell P. Antigen recognition by T lymphocytes. *Immunol Today* 1987; **8**: 67.
12. Farr AG, Kiely J-M, Unanue ER. Macrophage–T cell interactions involving Listeria monocytogenes – role of the H-2 gene complex. *J Immunol* 1979; **122**: 2395–404.
13. Hershman MJ, Cheadle WG, Wellhausen SR, Davidson PF, Polk HC Jr. Monocyte HLA-DR antigen expression characterises clinical outcome in the trauma patient. *Br J Surg* 1990; **77**: 204–7.
14. Shirakawa F, Yamashita U, Suzuki H. Decrease in HLA-DR positive monocytes in patients with systemic lupus erythematosus (SLE). *J Immunol* 1985; **134**: 3560–2.
15. Cheadle WG, Hershman MJ, Wellhausen SR, Polk HC Jr. HLA-DR antigen expression on peripheral blood monocytes correlates with surgical infection. *Am J Surg* 1991; **161**: 639–45.
16. Gibbons RA, Martinez OM, Lim RC, Horn JK, Garavoy MR. Reduction in HLA-DR, HLA-DQ, HLA-DP expression by Leu M3$^+$ cells from the peripheral blood of patients with thermal injury. *Clin Exp Immunol* 1989; **75**: 371–5.
17. Stephan RN, Conrad PJ, Janeway CC, Geha AS, Baue AE, Chaudry IH. Hemorrhage without significant tissue trauma produces immunosuppression and enhances susceptibility to sepsis. *Arch Surg* 1987; **122**: 62–8.
18. Ayala A, Perrin MM, Chaudry IH. Defective macrophage antigen presentation following haemorrhage is associated with the loss of MHC class II (Ia) antigens. *Immunology* 1990; **70**: 33–9.
19. Ayala A, Perrin MM, Wagner MA, Chaudry IH. Enhanced

susceptibility to sepsis after simple haemorrhage: depression of Fc and C3b receptor-mediated phagocytosis. *Arch Surg* 1990; **125**: 70–5.

20. Koziol JM, Rush BF, Smith SM, Machiedo GW. Occurrence of bacteremia during haemorrhagic shock. *J Trauma* 1988; **28**: 10–16.
21. Waymack JP, Fernandes G, Cappelli PJ *et al.* Alterations in host defense associated with anesthesia and blood transfusion. II. Effect on response to endotoxin. *Arch Surg* 1991; **126**: 59–62.
22. Hershman MJ, Polk HC Jr, Pietsch JD, Shields RE, Wellhausen SR, Sonnenfield G. Modulation of infection by gamma interferon treatment following trauma. *Infect Immun* 1988; **56**: 2412–16.
23. Hershman MJ, Appel SH, Wellhausen SR, Sonnenfield G, Polk HC Jr. Interferon-gamma treatment increases HLA-DR expression on monocytes in severely injured patients. *Clin Exp Immunol* 1989; **77**: 67–70.
24. Polk HC Jr, Cheadle WG, Livingston DH *et al.* A randomized prospective clinical trial to determine the efficacy of interferon-gamma in severely injured patients. *Am J Surg* 1992; **163**: 191–6.
25. Fischer H-G, Frosch S, Reske K, Reske-Kunz AB. Granulocyte–macrophage colony-stimulating factor activates macrophages derived from bone marrow cultures to synthesis of MHC class II molecules and to augmented antigen presentation function. *J Immunol* 1988; **141**: 3882–8.
26. Morrissey PJ, Bressler L, Park LS, Alpert A, Gillis S. Granulocyte–macrophage colony-stimulating factor augments the primary antibody response by enhancing the function of antigen-presenting cells. *J Immunol* 1987; **137**: 1113–19.
27. Cioffi WG, Burleson DG, Jordan BS *et al.* Effects of granulocyte–macrophage colony-stimulating factor in burn patients. *Arch Surg* 1991; **126**: 74–9.
28. Fertsch D, Schoenberg DR, Germain RN, Tou JYL, Vogel SN. Induction of macrophage Ia antigen expression by rIFN-γ and down-regulation by IFN-α/β and dexamethasone are mediated by changes in steady state levels of Ia mRNA. *J Immunol* 1987; **139**: 244–9.
29. Reynolds JV, Evantash E, Sigal R, Daly JM, Brady MP. Immune and endocrine effects of major abdominal operations. *Br J Surg* 1988; **75**: 1250A.
30. Janeway CC, Bottomly K, Babich J *et al.* Quantitative variation in Ia antigen expression plays a central role in immune regulation. *Immunol Today* 1984; **5**: 99–105.
31. Racioppi L, Moscarella A, Ruggiero G *et al.* Inhibition by anti-HLA class II monoclonal antibodies of monoclonal antibody OKT-3-induced T cell proliferation. Studies at the mRNA level. *J Immunol* 1990; **145**: 3635–40.
32. Santamaria P, Gehrz RC, Bryan MK, Barbosa JJ. Involvement of class II MHC molecule in the LPS-induction of IL1/TNF secretions by human monocytes. Quantitative differences at the polymorphic level. *J Immunol* 1989; **143**: 913–22.

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Diagnosis of traumatic rupture of the right hemidiaphragm by thoracoscopy

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Missed or delayed diagnosis of traumatic rupture of the diaphragm associated with blunt trauma remains frequent[1]. The diagnosis may be overlooked because of associated multiple injuries and, even with a high index of clinical suspicion, radiological investigation may be inconclusive. The advent of minimally invasive surgery has expanded diagnostic potential in both the abdomen and chest. A case of traumatic rupture of the right hemidiaphragm is presented in which a conclusive diagnosis was made at thoracoscopy.

Case report

A 36-year-old man was admitted from a peripheral hospital following a road traffic accident. His injuries included fractures of the right fifth, sixth and seventh ribs, L4 and sacrum, and an intertrochanteric fracture of the right hip. He also had a right haemothorax, which drained 1050 ml blood via a tube in the 3 days before transfer. Some 8 years previously the man had undergone total proctocolectomy with end ileostomy for ulcerative colitis, which was complicated by recurrent intra-abdominal sepsis. On admission he had a temperature of 38·2°C; the pulse rate was 100/min. Chest examination demonstrated dullness of the right base with bronchial breathing. The right leg was in a Thomas splint. Full blood count and general biochemical results were normal. Arterial blood gases showed hypoxia: the partial pressure of oxygen was 7·85 kPa and of carbon dioxide 5·14 kPa; the pH was 7·42. Chest radiography showed a generalized opacity in the right base that obscured the right hemidiaphragm. Abdominal ultrasonography was normal.

The patient was commenced on 1·2 g Augmentin (1 g amoxycillin plus 200 mg clavulanic acid; Beecham, Brentford, UK) intravenously three times daily and 40 per cent oxygen by face mask as treatment for right lower lung contusions and associated atelectasis. The following day he underwent internal fixation of the right hip fracture. At 3 days after admission repeat chest radiography clearly demonstrated an elevated right hemidiaphragm (*Figure 1*). Ultrasonographic examination could not confirm a diagnosis of ruptured hemidiaphragm. Intra-abdominal injection of 200 mBq ^{99m}technetium–tin colloid failed to demonstrate contrast in the chest as a result of previous adhesions.

As a diagnosis of ruptured right hemidiaphragm was still considered likely, the patient underwent right thoracoscopy. Under general anaesthesia using a double-lumen endobronchial tube, 1·5 litres carbon dioxide were introduced into the right pleural space following collapse of the right lung. A 0° laparoscope (Karl Storz, Tuttlingen, Germany) attached to an Olympus camera (OTV-S2; KeyMed, Dublin, Ireland) and imaging system was introduced through a 10-mm Surgiport (US Surgical, Norwalk, Connecticut, USA) cannula in the sixth intercostal space in the anterior axillary line. Using a blunt retractor introduced through a 5-mm cannula, the lung lobes were identified and retracted to demonstrate herniated liver in the chest cavity (*Figure 2*). A minithoracotomy incision was made through the seventh intercostal space, and repair of the diaphragmatic hernia was carried out using two layers of 0 Prolene (Ethicon, Edinburgh, UK) sutures. A tear in the pericardium extending along the phrenic nerve for 5 cm was also identified, indicating the possibility of concomitant phrenic nerve palsy. The patient was discharged 14 days later. The right hemidiaphragm remained elevated with no movement on screening, suggesting a persistent phrenic nerve palsy.

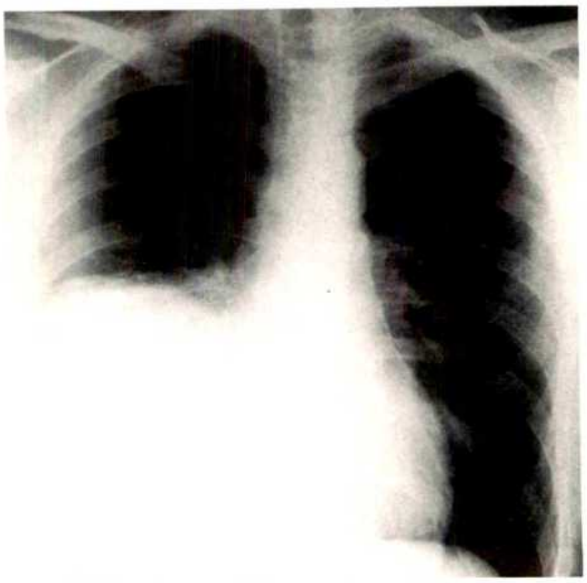

Figure 1 *Chest radiograph 6 days after admission, demonstrating an elevated right hemidiaphragm*

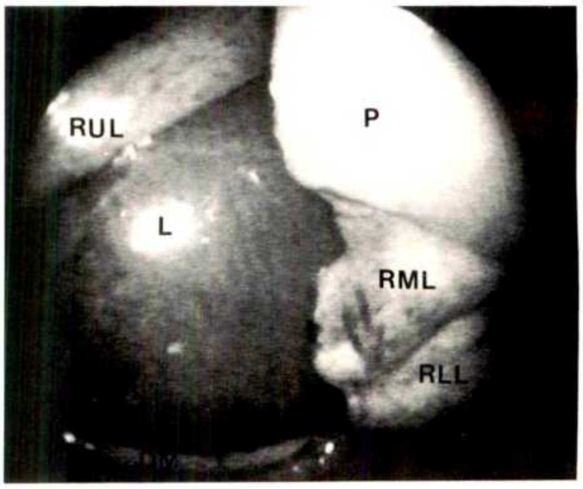

Figure 2 *Thoracoscopy showing herniated liver in the right chest cavity. RUL, right upper lobe of lung; RML, right middle lobe of lung; RLL, right lower lobe of lung; L, liver; DM, diaphragmatic margin; P, pericardium*

Discussion

This case typifies the diagnostic difficulties in confirming a ruptured right hemidiaphragm in the multiple trauma victim despite a high index of clinical suspicion. Conventional diagnosis rests on chest radiography showing a raised hemidiaphragm[2]. Although ultrasonography is frequently helpful[3], a conclusive diagnosis may be difficult. Computed tomography may also be useful, but difficulty can arise in delineating the diaphragm from the liver with right-sided ruptures[4]. Other diagnostic options include magnetic resonance imaging, which still requires further evaluation, and injection of radionuclide tracers into the abdomen, which was unsuccessful here because of postoperative adhesions.

Diagnostic laparoscopy can be useful and, in the case of suspected injuries to other abdominal organs, may be the preferred endoscopic diagnostic aid. Contraindications to laparoscopy may include previous abdominal operations or associated thoracic and cerebral injuries. Arendrup and Jensen have commented on the theoretical usefulness of thoracoscopy

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in the identification of diaphragmatic hernia but have not reported any personal experience[5]. The present case confirms the ease and usefulness of thoracoscopy in the evaluation of the patient with trauma. Experience in this case would suggest that thoracoscopy should be considered when conventional radiological measures are unhelpful in the diagnosis of traumatic rupture of the diaphragm.

References

1. Grimes OF. Traumatic injuries of the diaphragm. *Am J Surg* 1974; **128**: 175–81.
2. Johnson CD. Blunt injuries of the diaphragm. *Br J Surg* 1988; **75**: 226–30.
3. Somers JM, Gleeson FV, Flower CD. Rupture of the right hemidiaphragm following blunt trauma: the use of ultrasound in diagnosis. *Clin Radiol* 1990; **42**: 97–101.
4. McElwee TB, Myers RT, Pennell TC. Diaphragmatic rupture from blunt trauma. *Am Surg* 1984; **50**: 143–9.
5. Arendrup HC, Jensen BS. Traumatic rupture of the diaphragm. *Surg Gynecol Obstet* 1982; **154**: 525–30.

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Surgical workshop

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Easy technique for cholangiography during laparoscopic cholecystectomy

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The authors routinely use operative cholangiography during laparoscopic cholecystectomy to establish the presence of choledocholithiasis, which is then dealt with endoscopically, and to define the bile duct anatomy, preventing bile duct injury. The Tilley–Lichtwitz trocar and cannula (Downs Surgical, Sheffield, UK), commonly used for maxillary antral lavage, facilitate the placing of a ureteric catheter into the cystic duct.

Surgical technique

The Tilley–Lichtwitz trocar and cannula are introduced through the abdominal wall under direct vision, in the mid-clavicular line, just under the ribs. A no. 4 ureteric catheter snugly fits a 7-Fr cannula and a no. 5 catheter an 8-Fr cannula (*Figure 1*). The ureteric catheter can then be directed easily using the metal cannula aimed towards the cystic duct; the latter is then cannulated in the normal way.

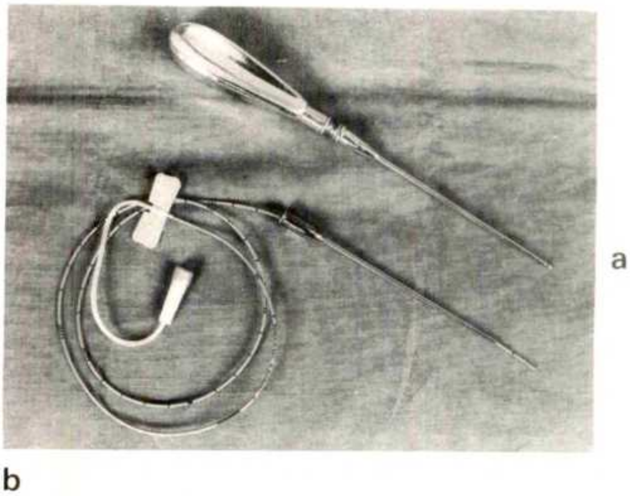

Figure 1 **a** *Tilley–Lichtwitz trocar and cannula.* **b** *A ureteric catheter with attached 'butterfly' is seen placed through the cannula, the trocar having been removed*

Discussion

The use of this instrument allows easy placement of the cholangiogram catheter within the abdominal cavity and the rigidity of the metal cannula is useful in facilitating manipulation. Its use in preference to a disposable intravenous cannula is recommended.

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Case report

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Pneumoperitoneum from a ruptured bronchus in a child

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Multiple injuries, especially those to the thorax, are rare in children. The most common causes are road traffic accidents, bicycle falls, falls from heights and non-accidental injuries. Pneumoperitoneum without abdominal visceral injury is rarely reported in the literature and is due mainly to pulmonary injury caused by barotrauma. Such an association has been reported infrequently in children[1,2].

Case report

A 10-year-old boy was admitted with multiple injuries. He had been riding his bicycle down a steep hill when he failed to control the speed on approaching a corner and crashed. The boy was found unconscious, straddled across and through a hedge. During the ambulance journey to hospital he suffered a respiratory arrest from which he was resuscitated. On arrival at the accident and emergency department the boy was unconscious with no response to painful stimuli but no focal neurological signs. He had bilateral poor air entry on auscultation of the chest, with shallow breathing. Surgical emphysema was noted in the neck, extending down over the upper chest, and separately over the lower abdomen limited distally by the attachments of Scarpa's fascia. Other injuries included a 15-cm full-thickness scalp laceration in the right parieto-occipital region and lacerations to the penile skin and right knee.

On arrival the boy was intubated and venous access was secured. Resuscitation was commenced with infusion of plasma and crystalloids. Immediate radiological investigation revealed a bilateral tension pneumothorax. Bilateral chest drains were inserted with full re-expansion of both lungs and no further air leakage. Abdominal examination showed an expanding abdominal girth with surgical emphysema in the groin and scrotum. Four-quadrant abdominal aspiration revealed air but no bile or blood, and an abdominal drain was inserted in the left iliac fossa. Findings at initial computed tomography (CT) of the head on admission were normal; abdominal CT showed no visceral injury and confirmed the plain radiographic findings (*Figure 1*) of air in the peritoneal cavity. In view of the distribution of abdominal gas, air was presumed to have tracked retroperitoneally from the mediastinum, and a conservative policy was adopted.

The patient remained stable; air continued to drain from the abdomen for 20 h. Some 48 h after admission he developed consolidation of the left lung which, in spite of intensive physiotherapy, failed to re-expand. Fibreoptic bronchoscopy showed blood in the left main bronchus, and rupture was diagnosed. At thoracotomy a complete transection of the left main bronchus was found and repaired.

After this the patient made a gradual improvement with pulmonary re-expansion; he remained intubated for 10 days. The pneumoperitoneum and surgical emphysema resolved slowly over 6 days following the initial trauma. The boy was well enough to be discharged 3 weeks after the accident and has remained well since.

Discussion

This child sustained major multiple injuries that needed intensive resuscitation and management. Two unusual signs were noted. First, bilateral tension pneumothorax is rare with a ruptured main bronchus[3]. The clinical course shows that full aeration of a lung can be maintained for 48 h in the presence of a complete bronchial rupture, unless it was the case that at first the rupture was incomplete. If this were so, consolidation in the left lung 48 h later coincided with complete detachment. This presentation has not been reported before.

The second unusual sign was the rapidly expanding pneumoperitoneum. This was almost certainly caused by the barotrauma with air tracking from the mediastinum behind the diaphragm into the retroperitoneal tissues and then rupturing into the peritoneal cavity. Air also tracked round the pelvis and into the lower abdominal wall tissues, being confined by Scarpa's fascia.

Earlier endoscopy would have led to confirmation of the clinically suspected ruptured bronchus sooner. At the time it was felt that initial maintenance of full expansion of the left lung justified the approach, especially when associated with a severe head injury.

Although such an association of thoracic injury and pneumoperitoneum is well recognized in adults[4,5], its rare occurrence warrants a reminder that it can occur in children.

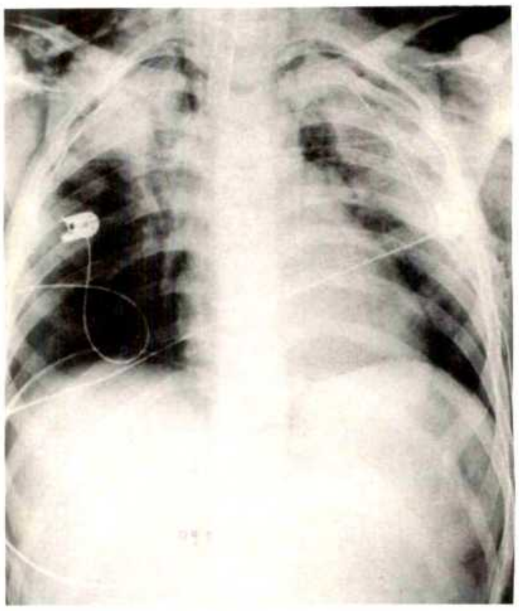

Figure 1 *Radiograph showing extensive surgical emphysema and air under the diaphragm*

References

1. Andrew TA, Milne DD. Pneumoperitoneum associated with pneumothorax or pneumopericardium: a surgical dilemma in the injured patient. *British Journal of Accident Surgery* 1979; **11**: 65–70.
2. Gregory K, Luna MD, Eddy AC. Traumatic pneumoperitoneum following combined abdominal and thoracic injury. *Pediatr Emerg Care* 1988; **4**: 30–1.
3. Spencer JA, Rogers CE, Westaby S. Clinico-radiological correlates in rupture of the major airways. *Clin Radiol* 1991; **43**: 371–6.
4. Sklar DP, Tandberg D, Weaver W. Thoracic stab wound with delayed pneumoperitoneum and pneumomediastinum. *Ann Emerg Med* 1984; **13**: 371–3.
5. Barnhart GR, Brooks JW, Kellum JM. Pneumoperitoneum resulting from tracheal rupture following blunt chest trauma. *J Trauma* 1986; **26**: 486–8.

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Resuscitation for haemorrhagic shock

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Hypovolaemic shock represents a major threat to the life of the patient suffering from post-traumatic or spontaneous haemorrhage, be it external or internal. Most modern clinicians were brought up with the belief that aggressive fluid resuscitation is the first priority until definitive control of the source of haemorrhage is achieved. Such an approach, currently advocated by the advanced trauma life support course of the American College of Surgeons Committee on Trauma, emphasizes that all hypotensive patients with suspected acute bleeding should be promptly treated with intravenous fluids to restore normal blood pressure before operative intervention. The rapid restoration of normovolaemia, it is preached, ought to sustain vital organ function during the acute phase and to play a role in the prevention of the delayed septic sequelae of severe shock.

This prevalent clinical practice is based on physiological experimental studies from the 1950s. The model of controlled haemorrhage depended on withdrawing blood atraumatically through a surgically inserted cannula to a predetermined endpoint of volume or pressure for a set time[1]. Unfortunately, this controlled bloodletting does not at all resemble the uncontrolled clinical situation in which blood pours out of injured or eroded vessels. The fundamental dissimilarity between experimental controlled haemorrhagic shock and clinical uncontrolled shock has recently raised a wave of renewed attention to this condition, reflected in clinical observations and novel experimental work, calling for critical reassessment of present policies of aggressive fluid resuscitation.

During World War I, Cannon and others, after observing combat casualties, concluded:

> 'Hemorrhage in the case of shock may not have occurred to a marked degree because blood pressure has been too low and flow too scant to overcome the obstacle offered by a clot. If the pressure is raised before the Surgeon is ready to check any bleeding that may take place, blood that is sorely needed may be lost'[2].

Following World War II it was stated:

> 'When internal hemorrhage persisted, for instance, there could be no resuscitation without surgery and it was wasteful of both time and blood to attempt to raise the patient's blood pressure to normal before operation. The blood or plasma which was administered merely leaked into the traumatized regions and was wasted, while at the same time the patient was submitted to the hazard of an unnecessary number of transfusions. Surgery, with control of the hemorrhage, was the simplest and the most effective way of accomplishing full resuscitation in such a case'[3].

The same concern was raised again by others who claimed that generous crystalloid resuscitation could be harmful in patients whose source of bleeding was not promptly controlled[4].

Autoregulatory mechanisms that control haemorrhage are important for homoeostasis. Hypotension slows bleeding and allows clot formation within the constricted vessel and its surroundings, which in turn leads to spontaneous cessation or reduction of bleeding. Experimental studies have demonstrated that the disruption of these defence mechanisms by drug-induced hypertension or treatment with anticoagulant agents tends to promote rebleeding from the lacerated vessel[5]. Recent experiments in animal models of uncontrolled haemorrhagic shock have clearly shown that resuscitation with Ringer's lactate[6] or hypertonic[7] solutions significantly increased both bleeding and death. Infusion-induced dilution of coagulation factors and hypothermia may contribute to clot disruption[8].

Clinical observation lends support to these experimental findings in the non-trauma situation. Crawford strongly believes that avoiding fluid and blood product resuscitation until the time of operation is a major factor behind his excellent results with ruptured aortic aneurysm. He claims that keeping the systolic blood pressure at 50–70 mmHg prevents clot dislodgement and increase in bleeding. Conversely, aggressive crystalloid infusion exaggerates haemorrhage before, during and after the procedure[9]. Others have suggested that excessive transfusion is associated with a higher incidence of further bleeding in patients suffering from upper gastrointestinal haemorrhage[10]. The priority of fluid resuscitation is also questioned by those who advocate a 'scoop and run' evacuation policy for severely injured patients.

Nevertheless, historical notes, clinical impressions and experimental animal data do not provide a definitive answer to the question of whether aggressive fluid resuscitation and restoration of blood pressure towards normal levels in the face of uncontrolled haemorrhage is deleterious to patients. A randomized clinical trial is needed to answer this crucial question.

Addendum

Since submission of this paper, results of a preliminary study of the type referred to have been published[11]; no significant difference in outcome between groups receiving delayed or immediate resuscitation was observed. The number of patients involved was, however, small, and further study of this issue is recommended.

References

1. Wiggers CJ. Experimental hemorrhage shock. In: Wiggers CJ, ed. *Physiology of Shock*. New York: Commonwealth Fund, 1950: 121–46.
2. Cannon WB, Fraser J, Cowell EM. The preventive treatment of wound shock. *JAMA* 1928; **70**: 618–21.
3. Beecher ME. Resuscitation of men severely wounded in battle. In: DeBakey ME, ed. *Surgery in World War II. Vol II: General Surgery*. Washington, District of Columbia: Office of the Surgeon General, Department of the Army, 1955: 6.
4. Wangensteen SL, Eddy DM, Ludewig RM. Bleeding and blood pressure. *Am J Surg* 1969; **118**: 413–14.
5. Shaftan GW, Chiu CJ, Dennis C, Harris B. Fundamentals of physiologic control of arterial hemorrhage. *Surgery* 1965; **58**: 851–6.
6. Bickel WH, Bruttig SP, Millnamov GA, O'Benar J, Wade CE. The detrimental effects of intravenous crystalloid after aortomy in swine. *Surgery* 1991; **110**: 529–36.
7. Gross D, Landau EH, Assalia A, Krausz MM. Is hypertonic saline resuscitation safe in 'uncontrolled' hemorrhagic shock? *J Trauma* 1988; **28**: 751–6.
8. Poole GV, Rhodes RS. Uncontrolled resuscitation. *Surgery* 1991, **110**: 573–4.
9. Crawford ES. Ruptured abdominal aortic aneurysm. *J Vasc Surg* 1991; **13**: 348–50 (Editorial).
10. Blair SD, Janvrin SB, McCollum CN, Greenhalgh RM. Effect of early blood transfusion on gastrointestinal haemorrhage. *Br J Surg* 1986; **73**: 783–5.
11. Martin RR, Bickell WH, Pepe PE, Burch JM, Mattox KL. Prospective evaluation of preoperative resuscitation in hypotensive patients with penetrating truncal injury: a preliminary report. *J Trauma* 1992; **33**: 354–62.

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Abdominal aortic thrombosis following a fall

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Abdominal aortic thrombosis following blunt trauma is rare. To date only 115 cases of thrombosis have been reported, caused mostly by dissection, rupture or transection[1,2]. A patient with aortic thrombosis following a fall is reported in whom there was no evidence of previous atheromatous disease. Only one previous case of aortic thrombosis related to lumbar vertebral injury has been described[3]. In that patient there was a lumbar fracture.

Case report

A 53-year-old psychiatric nurse was pushed by a patient and fell on to the buttocks. He sustained a crush fracture to the second lumbar vertebra and was admitted under the care of an orthopaedic surgeon. On admission the patient had no neurological deficit and was treated by bed rest and analgesia. There was no record of peripheral pulses. Some 12 days after the injury the patient suddenly developed pain, loss of sensation, and coldness in the left leg. On examination both femoral pulses were present, although the left was severely damped. No other lower-limb pulses were palpable and Doppler signals were unobtainable. Intra-arterial digital subtraction angiography showed a large filling defect in the infrarenal aorta extending into the left common iliac artery, with the aorta tapering distally. Emboli were seen in the right profunda femoris artery and left tibioperoneal trunk.

Embolectomy using a Fogarty catheter was performed through both common femoral arteries, and a thrombus removed from distal and proximal arteries. However, the inflow remained poor, so the aorta was exposed by a midline incision. There was no retroperitoneal haematoma or evidence of external aortic injury. An arteriotomy was made on the anterior aortic wall and a large thrombus removed from the distal aorta. There was no evidence of dissection, intimal flap or atheroma. The patient was given 10 000 units heparin intravenously during the procedure and was not administered anticoagulant after operation as he was under treatment for multiple peptic ulcers secondary to Zollinger–Ellison syndrome. An intraoperative arteriogram was satisfactory, showing good run-off; the patient made a complete recovery.

Echocardiography was normal, as was abdominal computed tomography specifically directed to find evidence of aortic injury.

Discussion

Blunt trauma of the abdomen resulting in aortic injury is rare. Aortic injury can follow road traffic accidents[4] and blunt trauma across the mid-abdomen. It is caused by rapid deceleration and shearing forces, which produce intimal tears, dissection and thrombosis. Traumatic aortic occlusion without dissection may occur in an atheromatous aorta with marked calcification, which reduces inherent resilience and elasticity. Traumatic thrombosis of the aorta without evidence of dissection, intimal tear or atheromatous disease occurred in the present patient and to the authors' knowledge has not been reported previously in the English literature. Aortic thrombosis is a rare complication of spinal injury that may require rapid diagnosis and management.

References

1. Matsaba J, Seko T, Ohta T, Shionya S, Ban I. Traumatic aneurysm of the abdominal aorta with acute thrombosis of bilateral iliac arteries. *Arch Surg* 1983; **118**: 1337–9.
2. Walker AG, Walker R. Traumatic thrombosis of the aorta. *BMJ* 1961; i: 1514.
3. Schaber FJ Jr. Aortic injury occurring after minor trauma in ankylosing spondylitis. *J Vasc Surg* 1986; 4: 410–11.
4. Welborn MB, Saumyers J. Acute abdominal aortic occlusion due to non-penetrating trauma. *Am J Surg* 1969; **118**: 112.

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Use of an accident and emergency department observation ward in the management of head injury

The management of 405 patients presenting with head injury to an accident and emergency department was assessed. Sixty-nine patients were admitted, although this number should have been 127 according to current guidelines on the management of head injury. Only three attenders were admitted inappropriately according to these guidelines. An accident and emergency observation ward was open on weekdays only; at weekends, patients with head injury were admitted to a general surgical ward. When the observation ward was open, 51 of the 76 patients (67 per cent) presenting with admission criteria were admitted. When closed, only 15 of the 51 patients (29 per cent) with these criteria were admitted. Guidelines were applied effectively to reduce the number of unnecessary admissions, but there was a significant number of patients with minor head injury who were discharged inappropriately. This number was much reduced when an observation ward was available.

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Many accident and emergency departments in the UK have an observation ward, managed by casualty officers, usually without help from other departments. Patients most suitable for treatment on such wards are those whose primary requirement is a short period of observation, without immediate need for specialist intervention, and whose condition usually results in discharge within 24 h.

Patients with minor head injury are ideally managed on an observation ward since they require a relatively short admission[1,2] and seldom develop serious consequences. The risk of developing haematoma and, therefore, of requiring specialist intervention is small: 1 in 121 for patients disorientated without skull fracture; 1 in 32 for those fully orientated with skull fracture[3]; and 0·59 per cent of those admitted[4]. Head injury causes 10 per cent of new accident and emergency attendances[5,6] and provides about one-quarter of all accident and emergency observation ward admissions[7–9]; 96 per cent of patients[7] stay <24 h.

This hospital's accident and emergency department has a 13-bed observation ward. Until recently, for financial reasons, the ward was closed at weekends, when patients with minor head injury had to be admitted via the surgical registrar to the main surgical ward.

Over the past 10–15 years much research has been performed to identify patients with seemingly minor head injury who have a significantly higher chance of requiring neurosurgical intervention[1,3–6,10–13]. In selecting only these high-risk patients for a period of observation, the number admitted can be reduced. Based on these research findings, in 1986 a Royal College of Surgeons of England working party published guidelines as to which patients with head injury should be admitted for observation[14]. This report recommended admission when certain easily defined criteria are present (*Table 1*). These criteria are listed on 'head injury forms' used at this and other accident and emergency departments.

This paper examines the incidence of these criteria in a typical population with head injury presenting to a London casualty department and audits the decision on admitting each patient for observation according to the recommended guidelines. Since the observation ward facility was not available for almost 3 days each week, with most other factors being constant, the unique situation arose of being able to apply these criteria to assess quantitatively whether the decision to admit a patient with head injury was more or less appropriate when an observation ward was available.

Table 1 *Incidence of criteria for admission in patients attending the accident and emergency department with head injury*

Criterion	No.
Confusion or any other depression of the level of consciousness at the time of examination	23 (5·7)
Skull fracture	9 (2·2)
Neurological signs or severe headache or vomiting	40 (9·9)
Difficulty in assessing the patient (e.g. alcohol, the young, epilepsy)	72 (17·8)
Other medical conditions (e.g. haemophilia)	1 (0·2)
The patient's social conditions or lack of responsible adult/relative	22 (5·4)

Values in parentheses are percentages of the 405 patients presenting

Patients and methods

The department is staffed by one consultant, two registrars and seven senior house officers. In this retrospective study, none of the examining doctors could have suspected audit, since no additional paperwork was requested from them. The records of 405 patients with head injury presenting between May and July 1991 were traced using the accident and emergency log book. All entries of 'head injury', 'laceration to head', 'assault', 'fall' and 'RTA' (road traffic accident) were analysed and the patients without head injury excluded; 14 sets of notes were not found. Children under 14 years of age and patients reattending were also excluded.

Each doctor's recorded history and examination findings in the notes and on the head injury cards was analysed. If the patient exhibited any of the signs or symptoms referred to in the Royal College guidelines as requiring admission, it was considered that the admission criteria had been met. It was then noted whether the patient had actually been admitted or not. Any self-discharges were treated as admissions, since this had been the clinician's original decision.

The date and time of each attendance was checked to establish whether the patient had presented when the observation ward was open or closed. This was performed once all data had been collected and analyses made, thus removing any observer bias. The admission of any patient presenting between 12.00 hours on a Friday and 06.00 hours on a Monday would have to have been via the surgical team to a surgical ward.

The proportion of patients being sent home 'inappropriately', that is with admission criteria, when the observation ward was open was calculated. This was compared with the proportion sent home when the observation ward was closed. Distribution of discrete variables was compared by the χ^2 test using Yates' continuity correction throughout.

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Results

A total of 405 patients presented with head injury over the 3-month period: 252 when the observation ward was open and 153 when closed. Of the 405 patients, 127 (31·4 per cent) exhibited criteria warranting admission. The incidence of each criterion is shown in *Table 1* (adding all incidences individually gives 167 as some of the 127 patients exhibited more than one criterion). The 'difficult to assess' criterion was the commonest, occurring in 72 patients, or 17·8 per cent of those presenting. Alcohol intoxication provided 64 of these, being present in 15·8 per cent of the cohort. This figure is lower than those of 22 and 46 per cent quoted by others[5,15], but for the purposes of the present study alcohol intoxication was defined as abnormal behaviour attributable to alcohol, and not simply a history of having consumed alcohol.

Table 2 shows that 61 of the 127 patients exhibiting one or more of the criteria warranting admission when seen by the casualty officer were sent home. Some of the reasons given for not admitting patients in this group were 'intoxicated and uncooperative', 'confusion probably postictal', 'vomiting but skull X-ray normal' and 'fully orientated with only hairline fracture'. Four patients presented again and were admitted for observation at a later date; all four had exhibited positive criteria when seen and discharged initially. An additional three patients were admitted without having met any of the criteria, the reasons given for admission being a history of 'amnesia', 'lost consciousness' and 'hit with axe'. (If the guidelines were adhered to strictly, these alone are indications for skull radiography, but not admission.)

Table 3 compares the management of patients with head injury depending on the availability of the observation ward. When the ward was open, 25 of the 76 patients with admission criteria (33 per cent) were sent home, whereas 36 of the 51 patients with admission criteria (71 per cent) were sent home when the ward was closed. This difference is significant ($\chi^2 = 15\cdot90$, 1 d.f., $P < 0\cdot001$). Of the 252 patients who presented when the ward was open, 21·4 per cent were admitted, but only 9·8 per cent of the 153 who presented when the ward was closed were admitted. This difference is also significant ($\chi^2 = 8\cdot30$, 1 d.f., $P < 0\cdot01$).

There was no significant difference in the proportion of patients exhibiting positive criteria when the ward was open (76 of 252) and when it was closed (51 of 153) ($\chi^2 = 0\cdot31$, 1 d.f., $P = 0\cdot58$); the two groups were equivalent in terms of injury severity.

Table 2 *Application of criteria to 405 patients to assess eligibility for admission*

Category	No.
Criteria met	
Admitted	66 (16·3)
Sent home	61 (15·1)
Total	127 (31·4)
No criterion met	
Admitted	3 (0·7)
Sent home	275 (67·9)
Total	278 (68·6)

Values in parentheses are percentages

Table 3 *Admission outcomes depending on observation ward availability*

Category	Ward open ($n = 252$)	Ward closed ($n = 153$)
Criteria met		
Admitted	51 (20·2)	15 (9·8)
Sent home	25 (9·9)	36 (23·5)
Total	76 (30·2)	51 (33·3)
No criterion met		
Admitted	3 (1·2)	0 (0·0)
Sent home	173 (68·7)	102 (66·7)
Total	176 (69·8)	102 (66·7)

Values in parentheses are percentages

Discussion

The results show that about 31 per cent of all patients attending the accident and emergency department with head injury exhibit one or more of the criteria that warrant admission. However, only 17 per cent of the total were admitted, which shows discordance between the practice recommended in the guidelines and that of the casualty officers. This difference was far more marked when the observation ward was closed.

One might attribute the low overall admission rates to selection errors made by casualty doctors, but only three of the 405 patients were admitted inappropriately, which suggests that the guidelines are being adhered to, at least as far as preventing unnecessary admission. The authors cannot condemn the admission of only three patients at the discretion of the clinician as each case is individual and it may be that other factors were considered, for instance, the higher risk associated with penetration of the galea[16] in the patient 'hit with axe'. The low overall figure is an improvement on a study of head injury cases made just before the publication of these[14] and similar[12] guidelines, which revealed that up to 20 per cent of those admitted in nine different centres did not fulfil admission criteria[17].

The significant variation in compliance with the guidelines according to availability of the observation ward suggests this may be an important factor. Admitting a patient formally to a surgical ward usually requires review by two more clinicians from the surgical team and, since the observation ward is closed at unsociable times, there may be reluctance to waken or disturb colleagues. Admitting surgical registrars are also under great pressure to keep beds empty to avoid cancellation of routine lists. This pressure may be great in this hospital since it is a National Health Service Trust.

The 31 per cent admission rate resulting from proper application of the guidelines to this series of patients with head injury would have resulted in an admission rate 14 per cent higher than that which actually occurred. This represents an extra 227 admissions a year in this hospital. A 31 per cent admission rate is also higher than rates of 15–28 per cent previously reported in other studies[5,15,17] and it may be that further refinement of the guidelines will reduce this number and result in greater correlation with actual clinical practice. Another solution would be to allow more patients with borderline criteria to undergo close observation at home by responsible relatives. This is being initiated by giving all discharged head-injured patients a list of signs or symptoms that are of concern, but it is not suitable if observation is required throughout the night.

This study has shown that guidelines have been successful in reducing the number of inappropriate admissions. However, there is now a situation in which only 52 per cent of patients with admission criteria are actually admitted. The fact that the proportion is more than halved when an accident and emergency department observation ward is not available suggests that bed availability and ease of admission are more important factors than recognized signs and symptoms. Guidelines were introduced to aid clinicians, but these may now be detrimental if they recommend admissions that are too great in number or impractical in nature. This discordance may be partly overcome by the wider use of observation wards or by future development of more stringent admission criteria. Otherwise, clinicians will continue to send patients home with signs or symptoms that warrant admission according to advice from an established 'panel of experts', action that is a danger medically to the patient and medicolegally to the clinician.

References

1. Dacey RG, Wayne MA, Rimel RW *et al.* Neurosurgical complications after apparently minor head injury. *J Neurosurg* 1986; **65**: 203–10.
2. Conrad L, Markovchick V, Mitchiner J *et al.* The role of an emergency department observation unit in the management of trauma patients. *J Emerg Med* 1985; **2**: 325–33.
3. Mendelow AD, Teasdale G, Jennet B *et al.* Risks of intracranial haematoma in head injured adults. *BMJ* 1983; **287**: 1173–6.
4. Jones JJ, Jeffreys RV. Relative risks of alternate admission policies for patients with head injuries. *Lancet* 1981; i: 850–2.
5. Strang I, MacMillan R, Jennet B. Head injuries in accident and emergency departments at Scottish hospitals. *Injury* 1978; **10**: 154–9.
6. Jennet B, MacMillan R. Epidemiology of head injury. *BMJ* 1981; **282**: 101–4.
7. Maimaris C, Kirby NG. The impact of the observation ward on acute admissions at Guy's Hospital. *Health Trends* 1991; **23**: 33–5.
8. Morgan WJ. Functions of the observation ward in the accident and emergency department. *BMJ* 1981; **282**: 398–9 (Letter).
9. Dallos V, Mouzas GL. An evaluation of the functions of the short stay observation ward in the accident and emergency department. *BMJ* 1981; **282**: 37–40.
10. Weston PA. Admission policy for patients following head injury. *Br J Surg* 1981; **68**: 663–4.
11. Mendelow AD, Campbell DA, Jeffrey RR *et al.* Admission after mild head injury: benefits and costs. *BMJ* 1982; **285**: 1530–2.
12. A group of neurosurgeons. Guidelines for initial management after head injury in adults. *BMJ* 1984; **288**: 983–5.
13. Miller JD, Murray LS, Teasdale GM. Development of traumatic intracranial haematoma after a 'minor' head injury. *Neurosurgery* 1990; **27**: 669–73.
14. Royal College of Surgeons Working Party – Commission on the Provision of Surgical Services. *Report of the Working Party on Head Injuries.* London: Royal College of Surgeons, 1986.
15. Swann IJ, MacMillan R, Strong I. Head injuries at an inner city accident and emergency department. *Injury* 1981; **12**: 274–8.
16. Ballantyne E, Mendelow AD, MacMillan R, Brookes M. Relationships between scalp wounds and skull fractures. *IRCS Medical Science* 1986; **14**: 63–4.
17. Fowkes FGR, Ennis WP, Evans RC *et al.* Admission guidelines for head injuries: variance with clinical practice in accident and emergency units in the UK. *Br J Surg* 1986; **73**: 891–3.

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Helicopter Emergency Medical Service operating from the Royal London Hospital: the first year

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The additional workload on the support hospital created by using a helicopter for emergency trauma has been assessed in the first year of operation. A total of 135 patients were brought to the Royal London Hospital, of whom 30 died, 34 were transferred for convalescence or rehabilitation to another hospital, and 71 discharged home. The median Injury Severity Score was 17 (range 0–75) and 82 patients (60·7 per cent) had a reduced Revised Trauma Score at the scene. Blunt injury greatly outnumbered penetrating trauma (117 versus *15 patients). Accidental injuries accounted for 77·0 per cent of the total, self-inflicted wounds 14·1 per cent and assaults 8·9 per cent. Parameters employed to assess workload were hospital bed-days used (total 2361), operations (118, occupying 287 h of theatre time) and blood transfusion (total 702 units used). The second 6-month study period showed a considerable increase in the number of patients admitted (102* versus *33) because of increased efficiency in call-out procedures.*

A report in 1988 by The Royal College of Surgeons of England[1] called attention to the deficiencies of trauma treatment in the UK and called for the creation of trauma centres. To date one such centre (Stoke-on-Trent) has been funded for a trial period. Guidelines for systems of trauma care were laid down by the American College of Emergency Physicians[2] and revised in 1987. In the same year Shackford *et al.*[3] reported that a trauma system improved survival in severely injured patients and this was attributed to the integration of prehospital and hospital care with expeditious surgery.

A number of European countries have instituted systems enabling early medical intervention at the scene of an incident. In France and Germany these systems are supplemented by helicopters. The German system was considered outstanding by Trunkey[4].

Patients arriving at the Royal London Hospital with serious injury are received by a trauma team working on the principles of advanced trauma life support[5] led by consultant or senior registrar surgeons trained in these principles. Many of these patients now arrive via the Helicopter Emergency Medical Service (HEMS), which is fully integrated into the hospital system and London Ambulance Service emergency call-out system.

The helicopter service has completed its first 12 months of operation using the landing pad on the roof of the Royal London Hospital. This paper considers the types of patient admitted and the subsequent workload imposed on the hospital.

The helicopter system was instituted solely for the treatment of trauma[6]. The aircraft (Dauphin SH 365H; Aerospatiale, Marignane, France) is based, during daylight hours, on a purpose-built helipad constructed on the roof of a building that contains operating theatres and the accident and emergency department. These areas are linked by a dedicated lift. The aircraft is activated through the London Ambulance Service control room. The system is unique in the UK in that the aircraft carries a doctor on all missions. It is extensively equipped with removable monitoring and intensive care equipment that enables roadside and in-ambulance monitoring and treatment. A paramedic accompanies the doctor and the aircraft has a pilot and co-pilot.

The Royal London Hospital already had all the necessary specialities for trauma care (other than a burns unit), including neurosurgery and cardiothoracic surgery. The Department of Health funded an additional eight beds for the project including all necessary staff. The cost of the aircraft was borne by Express Newspapers.

Patients and methods

Missions and admissions

Between September 1990 and August 1991 a total of 1077 missions were flown. *Table 1* grades the missions according to the highest category pertaining to each flight.

The 250 'A' category missions resulted in 135 patients being brought to the hospital. Of these, 124 were carried by helicopter and 11 brought in by road ambulance after the aircraft had attended the incident. These 11 patients were all accompanied by the helicopter service doctor with monitoring and treatment maintained to the same standard as would have pertained in the aircraft, and are included in this study. The remaining A category missions resulted in 126 patients being similarly transported to other suitable hospitals. A summary of the patients admitted to the Royal London Hospital is shown in *Table 2*.

Table 1 *Helicopter Emergency Medical Service missions, September 1990 to August 1991*

	Mission category*					
	A	B	C	D	Total	Percentage aborted
1990						
September	8	4	15	44	71	62
October	10	14	22	60	106	57
November	3	1	6	12	22	55
December	7	3	13	26	49	53
1991						
January	9	5	25	42	81	52
February	11	8	18	32	69	46
March	20	6	28	83	137	61
April	34	5	35	56	130	43
May	41	4	31	36	112	32
June	31	3	37	40	111	36
July	42	6	19	32	99	32
August	34	5	31	20	90	22
Total	250	64	280	483	1077	

*A, mission resulting in a patient flown or escorted to a hospital as a primary rescue; B, interhospital transfer; C, patient treated on the ground and sent to hospital or declared dead at scene; D, mission aborted

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Table 2 *Details of 135 patients admitted to the Royal London Hospital*

Sex ratio (M:F)	95:40
Age (years)	
<16	33
≥ 55	15
Median (range) ISS (based on AIS 90)	17 (0–75)
Reduced Revised Trauma Score at scene	82
Blunt injury*	117
Penetrating injury*	15
Multiregional injuries†	78
Head injury (AIS ≥ 3)	63
Died	30

ISS, Injury Severity Score; AIS 90, Abbreviated Injury Score, 1990 edition. *Three patients were not classified as having a blunt or penetrating injury (one near drowning, one smoke inhalation, one toxic gas inhalation); †injuries of AIS >2 in each of two or more AIS body regions

Table 3 *Mechanisms of injury in 135 patients*

	No. of patients
Accidental	
Road traffic accident	
Pedestrian	37
Vehicle occupant	22
Motor cyclist	5
Cyclist	4
Fall	23
Other	13
Total	104 (77·0)
Self-inflicted	
Jump from height	12
Other	7
Total	19 (14·1)
Assault	
Stabbing	8
Gunshot wound	4
Total	12 (8·9)

Values in parentheses are percentages

The helicopter service doctor decided which hospital the patient should go to and whether this would be by land or air, accompanied or not. Protocols were developed based on those of Champion[7]; physiological parameters, mechanism of injury and apparent anatomical injuries were used as predictors of the level of risk to the patient. With a high risk of serious injury the patient will benefit from treatment at a multidisciplinary centre. Details of nearby hospitals were available to the HEMS doctor, including distances from the scene of the incident and the specialities available. Patients not admitted to the Royal London Hospital will be included in the independent evaluation.

Admission rates to the Royal London Hospital increased from 33 in the first 6 months to 102 admissions in the second period, although there were no statistical differences with respect to sex, age, blunt or penetrating injury, multiple trauma, head injury or Injury Severity Score (ISS).

Injuries

There was a preponderance of blunt injuries over penetrating wounds. The ISS was measured using the Abbreviated Injury Score, 1990 edition (AIS 90)[8]. Three patients (one near drowning, one suffering from smoke inhalation, one from toxic gas inhalation) could not be scored by this method. In the remaining patients the range was 0–75. The median ISS was 17; 76 patients (56·3 per cent) had ISS scores ≥ 16, the usual definition of serious injury. Eighty-two patients (60·7 per cent) had a reduced initial Revised Trauma Score (RTS)[9] at the scene. In all, 98 patients (72·6 per cent) had a reduced RTS and/or ISS ≥ 16. The mechanisms of injury are shown in *Table 3*.

Workload and staffing

Bed occupancy, operating theatre times and the use of blood products were measured as parameters of workload. An additional number of staff were employed to enhance support to the helicopter service. The pilots' and controllers for the aircraft are employed by Express Newspapers and the paramedics by the London Ambulance Service. Thirteen nurses staffed the four-bed trauma unit. Although the most critically injured patients were still admitted to the intensive care unit, the trauma unit was equipped to deal with a similar severity of injury. During the period of study the equipment was enhanced so that all beds could accommodate patients undergoing ventilation. Five nurses augmented the staff of the intensive care unit; two were deployed to the accident and emergency department and one each to the renal unit and paediatric department. Four additional nurses were supported on the ENB199 (accident and emergency) course and a further four, awaiting the start of the next course, occupied rotational posts in various departments. A medical laboratory scientific officer was employed in the blood transfusion laboratory.

Results

Of the 135 patients, 11 died in the accident and emergency department and five in the intensive care unit within 6 h of admission. A further two patients were transferred to other hospitals direct from the accident and emergency department, one to a psychiatric hospital and one to her local hospital having been brought from a rural area to the Royal London Hospital only because the local hospital was fog bound. One patient, an infant, was admitted with her mother having been involved in a road traffic accident but proved to be unhurt and was discharged a few hours later. These 19 patients were excluded from the bed occupancy figures shown in *Table 4* to give data on 116 patients.

It was originally envisaged that a total of eight beds would be available (one on the intensive care unit, four on the trauma unit, three on general wards) but the mean occupancy was 6·5 beds. In the first 6 months the mean was 3·7 beds but rose to 9·2 beds in the second period, with a maximum on one day of 15.

Of the 116 patients admitted, 14 died, 32 were transferred to other hospitals and 70 were discharged home. During the period under consideration 71 patients (52·6 per cent) required surgery, undergoing a total of 118 operations (emergency and subsequent) amounting to 287 h of theatre time.

A detailed study of operating times was undertaken for the last 4 months of the study period, during which 66 patients were admitted and 38 (58 per cent) underwent surgery. A total of 59 operations were performed (*Table 5*). Times were taken

Table 4 *Bed occupancy for 116 patients*

	Intensive care unit	Trauma unit	General ward	Overall
Patients admitted	41	83	86	116
Total bed-days	160	523	1678	2361
Patient stay (days)				
Mean	3·9	6·3	19·5	20·4
Maximum	19	22	231	248
Median	2	5	10	10

Table 5 *Operations on 38 patients brought in by the Helicopter Emergency Medical Service in the 4 months from May to August 1991*

Speciality	No. of operations	Operating time (h min)
Orthopaedics	22 (37)	59 35 (38·3)
Neurosurgery	15 (25)	36 20 (23·4)
General	10 (17)	15 30 (10·0)
Maxillofacial	6 (10)	16 40 (10·7)
Transplant (organ harvesting)	1 (2)	4 40 (3·0)
Cardiothoracic	1 (2)	2 40 (1·7)
Plastic	1 (2)	1 15 (0·8)
Multidisciplinary	3 (5)	18 45 (12·1)
Total	59 (100)	155 25 (100)

Values in parentheses are percentages

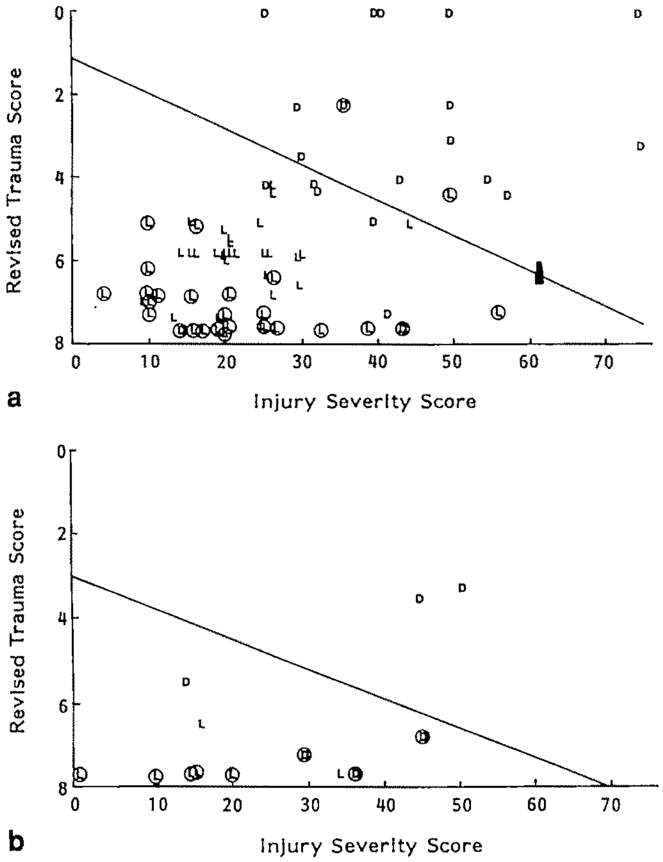

Figure 1 *Blunt injuries in patients aged* **a** *<55 years and* **b** *≥ 55 years. L, alive on discharge or at 3 months; D, dead. Circled patients are those with a Revised Trauma Score (RTS) estimation on arrival in hospital. (For clarity, 32 survivors with RTS 7·84 and Injury Severity Score <16 have been omitted)*

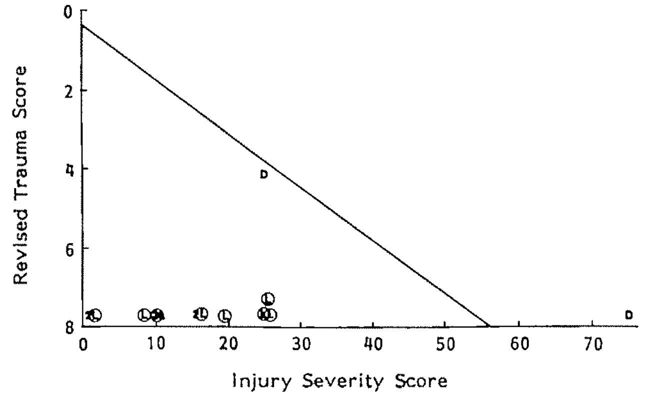

Figure 2 *Penetrating injuries in patients <55 years of age. L, alive on discharge or at 3 months; D, dead. Circled patients are those with a Revised Trauma Score on arrival in hospital*

from induction of anaesthesia to leaving theatre; the recovery room period was not included. Of the 38 patients undergoing surgery in these 4 months, ten (26 per cent) had their first operation performed by a consultant surgeon, 17 (45 per cent) by a senior registrar and 11 (29 per cent) by a registrar. Thirty-three patients had surgery within 24 h and 22 within 4 h of admission.

Eighty-six patients required blood transfusion, using a total of 702 (range 1–49, median 4·5) units. In all, 117 patients had blood cross-matched involving a total issue of 1229 units. Of the blood issued 57·1 per cent was used. Fresh frozen plasma was used in 30 patients (146 units) and 99 units of platelets were used in 11 patients. Four patients received cryoprecipitate: two received 6 units each, one received 20 units and one 24 units; each of these patients died. All patients admitted via the HEMS were subject to audit procedures, including trauma and injury severity scores (TRISS) methodology[10] (*Figures 1* and *2*). Only two patients aged 55 years or more received penetrating injuries and both survived. The RTS is normally calculated in the accident and emergency department when using TRISS methodology; however, in the present series this was not always possible. Fifty-two patients (38·5 per cent) arrived ventilated, thus rendering the RTS incalculable; data for these patients, plus four for whom the hospital information was incomplete, have been plotted using the 'at-scene' data. Of the 79 patients shown with an 'in-hospital' RTS, 44 had no change between the 'at-scene' and 'hospital' scores, 12 had a reduced score and the score of 23 had improved with treatment. Of the 44 unchanged scores, 41 were normal throughout.

Discussion

The effect of superimposing a helicopter service on a busy teaching hospital is significant. Preparatory enhancement of plant and staff resources is essential. Since the study period an extra occupational therapist has been recruited because of the importance of rehabilitation. Although a large proportion of patients are transferred to local hospitals or special units for continuation of rehabilitation, a considerable number remain within the Royal London Hospital for the majority of this treatment phase. There will be a reappraisal of staff levels to ensure a more appropriate distribution of the additional staffing.

The high level of self-inflicted injury seen in this study creates additional difficulties because surviving patients require psychiatric and social work support. This is in addition to the normal help offered to victims of serious accidents for stress disorders. Adequate psychiatric cover is essential to centres dealing with large numbers of patients with trauma and there is a need for counselling of staff at all levels because the stress of dealing with the seriously injured is significant.

Once the system had 'settled down' in the second 6-month period there was a mean of 17 patients per month admitted via the helicopter service. During the same period, a total of 1116 patients with trauma were admitted to the Royal London Hospital. The helicopter service patients thus represented 9·1 per cent of those with trauma admitted but had a disproportionately large impact on the system.

The amount of surgery required was considerable; some 50 per cent of patients underwent surgery within 24 h, and one-third were operated on within 4 h of admission. This raises the question of the provision of an operating theatre specifically designated for emergencies. If the 4-month period studied in detail is typical, then the annual theatre usage would be approximately 180 operations occupying 470 h of theatre time.

Some 70 per cent of all first operations were performed by consultants or senior registrars (over 75 per cent for those undertaken within 4 h of admission). In 25 per cent of cases the first operation was performed by a consultant surgeon; this value compares well with the 5·6 per cent reported by the working party of The Royal College of Surgeons[1] in 1988.

The laboratory workload has been evaluated only in terms of blood transfusion and blood products. Extrapolating the results from the second half of the year, an annual blood use of around 1000 units could be envisaged, requiring the cross-matching of 1800 units. The impact of the helicopter service on other parts of the hospital is considerable, particularly for the radiology, anaesthesia and biochemistry departments.

TRISS methodology (*Figures 1* and *2*) was used as an audit to select patients in need of further investigation and is an essential component of the UK Major Trauma Outcome Study[11]. The Royal London Hospital has participated in this study since April 1991. There are a number of difficulties associated with the audit method, the principal of which is the time at which the RTS is estimated. The present rules require that the RTS be estimated from data obtained on arrival at hospital; once a patient has been intubated and ventilated the score can no longer be measured. Fifty-two of the patients in this study were ventilated by the HEMS doctor before arrival at the hospital. These represent the most seriously injured but would be excluded from the audit. Where possible the time course of the RTS was monitored: values in 44 cases were unchanged between the scene and hospital; of these, 41 were normal throughout. Twelve patients had decreased and 23 had improved values during the period of observation; all these had had some form of treatment, usually oxygen and intravenous infusion, thus it is not possible to determine what the RTS on arrival at hospital might have been without such intervention. The graphs should be viewed in the light of these observations. The UK Major Trauma Outcome Study has started to collect prehospital data and at some stage in the future it may be possible to recalculate survival probabilities based on prehospital observation of RTS.

References

1. Commission on the Provision of Surgical Services. *Report of the Working Party on the Management of Patients with Major Injuries.* London: Royal College of Surgeons of England, 1988.
2. American College of Emergency Physicians. Guidelines for trauma care systems. *Ann Emerg Med* 1987; **16**: 459–63.
3. Shackford SR, Mackenzie RC, Hoyt DB *et al.* Impact of a trauma system on outcome of severely injured patients. *Arch Surg* 1987; **122**: 523–7.
4. Trunkey DD. Presidential address: on the nature of things that go bump in the night. *Surgery* 1982; **92**: 123.
5. *Advanced Trauma Life Support (ATLS) Student Manual.* Chicago, Illinois: American College of Surgeons, 1989.
6. Earlam RJ, ed. *The Royal London Hospital Daily Express Helicopter Emergency Medical Service.* Bishops Stortford: Saldatore, 1992.
7. Champion HR. Field triage of trauma patients. *Ann Emerg Med* 1982; **11**: 160–5.
8. American Association for Automotive Medicine. *The Abbreviated Injury Scale, 1990 Revision.* Des Plaines, Illinois: American Association for Automotive Medicine, 1990.
9. Champion HR, Sacco WJ, Copes WS *et al.* A revision of the trauma score. *J Trauma* 1989; **29**: 623–9.
10. Boyce CR, Tolson MR, Copes WS. Evaluating trauma care: the TRISS method. *J Trauma* 1987; **27**: 370–8.
11. Yates DW, Woodford M, Hollis S. Preliminary analysis of the care of injured patients in 33 British hospitals: first report of the United Kingdom Major Trauma Outcome Study. *BMJ* 1992; **305**: 737–40.

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Short note

Br. J. Surg. 1993, Vol. 80, February, 222

A family with dual inheritance of primary hyperparathyroidism and haemophilia

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The coexistence of two distinct inherited diseases in one individual or family is rare. A family with a unique combination of inherited conditions, primary hyperparathyroidism and severe classical haemophilia, is described.

Case report

A 54-year-old man was referred for assessment of hypercalcaemia. He provided a complex medical history including myocardial infarction, cerebrovascular accident and peripheral vascular disease. The serum calcium level was 2·71 (normal range 2·25–2·50) mmol/l with a concomitant measurable serum parathyroid hormone concentration of 0·28 μg/l (*C*-terminal radioimmunoassay), confirming a diagnosis of hyperparathyroidism. The patient was not submitted to operation and died 6 years later from cardiac failure.

At referral the patient reported that one of his daughters had hypercalcaemia and that all three of his sons had severe haemophilia. All six of the patient's children attended for screening for hyperparathyroidism.

Results

The results of screening the offspring of the propositus are summarized in *Figure 1*. One sister and two brothers were found to have hyperparathyroidism and all three males were confirmed as having severe haemophilia. Neck exploration was advised in the three family members with hyperparathyroidism. Operation in the two brothers was covered by infusion of factor VIII concentrate.

At cervical exploration patients II.2, II.4 and II.5 underwent 3·5-, 3- and 3·5-gland subtotal parathyroidectomy respectively. Histological examination of the surgical specimens confirmed the presence of adenomatous hyperplasia. Current serum calcium levels remain normal 7, 1 and 5 years after operation.

Normal serum calcium levels were found on screening of siblings II.1, II.3 and II.6 and the two children of patient II.2 (patients III.1 and III.2).

Discussion

Sporadic hyperparathyroidism is a common disease[1]; familial hyperparathyroidism is seen much less often. The inheritance of familial hyperparathyroidism is believed to be autosomal dominant and the disease pattern in this family is in keeping with this hypothesis.

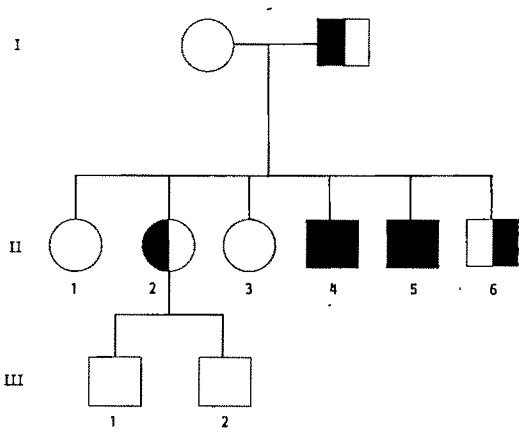

Figure 1 *Pedigree of a family with familial primary hyperparathyroidism and haemophilia.* ○, *Female;* □, *male;* ◧, *hyperparathyroidism;* ◨, *haemophilia*

The disease may result from solitary parathyroid adenoma[2], multiple adenomas[3] or multigland hyperplasia[4], the latter occurring most frequently. All three affected members in this family demonstrated multiple gland disease and were treated by subtotal parathyroidectomy rather than total parathyroidectomy with forearm autotransplantation[5].

When familial hyperparathyroidism is discovered, screening identifies additional affected family members. Many asymptomatic individuals with familial hyperparathyroidism eventually demonstrate complications[2,3] and cervical exploration is therefore justified in these circumstances.

The coexistence of familial hyperparathyroidism and haemophilia in this family is highly unusual. The concomitant presence of these two conditions within one family has probably occurred entirely by chance, each being inherited in a separate and unrelated fashion.

References

1. Christensson T, Hellstrom K, Wengle B, Alveryd A, Wikland B. Prevalence of hypercalcaemia in a health screening in Stockholm. *Acta Medica Scandinavica* 1976; **200**: 131–7.
2. Allo M, Thompson NW. Familial hyperparathyroidism caused by solitary adenomas. *Surgery* 1982; **92**: 486–90.
3. Cassidy CE, Anderson AS. A familial occurrence of hyperparathyroidism caused by multiple parathyroid adenomas. *Metabolism* 1960; **9**: 1152–8.
4. Cutler RE, Reiss E, Ackerman LV. Familial hyperparathyroidism: a kindred involving eleven cases with a discussion of primary chief-cell hyperplasia. *N Engl J Med* 1964; **270**: 859–65.
5. Wells SA, Gunnells JC, Shelburne JD, Schneider AB, Sherwood LM. Transplantation of the parathyroid glands in man. Clinical indications and results. *Surgery* 1975; **78**: 34–44.

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Phaeochromocytoma associated with thymoma

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Phaeochromocytomas may be associated with other neoplasms as part of the multiple endocrine neoplasia (MEN) syndrome. Two cases are described of phaeochromocytoma and thymoma occurring concurrently, an association that has not previously been reported.

Case reports

Patient 1

In April 1988, a 55-year-old man presented with a 2-week history of daily episodes of palpitations, severe headaches and sweating. The only abnormal finding was a blood pressure of 190/115 mmHg. Chest radiography suggested a small right hilar mass. Biochemical screening showed markedly raised urinary catecholamine levels with a vanillyl mandelic acid concentration of 240 μmol/l. Abdominal computed tomography (CT) demonstrated a 6-cm mass in the right adrenal gland involving the inferior vena cava (*Figure 1*). ^{131}I-*m*-iodobenzylguanidine (MIBG) scanning showed no uptake other than this, indicating that the shadow on the chest radiograph was probably not a metastasis. In July 1988, a benign phaeochromocytoma was uneventfully excised and the patient made a good recovery.

Over the next few months, the shadow on the chest radiograph increased in size. A low gamma globulin count was noted and acetylcholine receptor antibodies were weakly positive. In February 1989, an exploratory median sternotomy was performed and a benign thymoma was widely excised.

At 3-year follow-up there has been no recurrence of either tumour and the patient remains well.

Patient 2

In June 1986, a 47-year-old woman presented with a long history of intermittent sweating, chest pain and a weak voice. A mediastinal mass was discovered on chest radiography (*Figure 2*). On admission for anterior mediastinotomy, transient hypertension was noted. After operation frank myasthenia developed, initially requiring ventilation but responding well to pyridostigmine. Some 2 weeks later an uneventful median sternotomy was performed and an invasive thymoma was excised with difficulty.

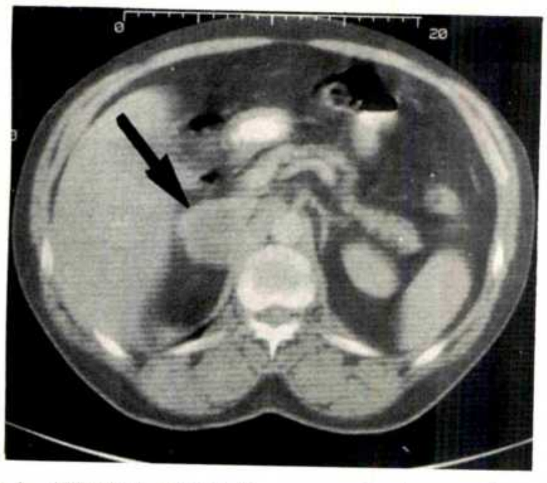

Figure 1 *Abdominal computed tomogram showing a right adrenal phaeochromocytoma (arrow)*

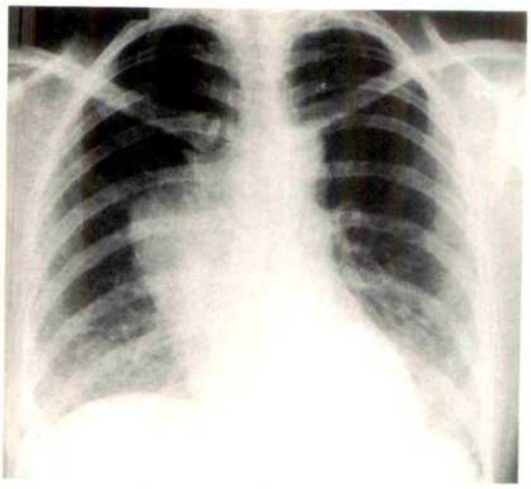

Figure 2 *Posteroanterior chest radiograph showing a large thymoma*

The myasthenia improved after operation but the episodes of sweating, agitation and hypertension continued, and eventually urinary catecholamine levels were found to be raised. CT and MIBG failed to localize the phaeochromocytoma, but selective venous sampling and digital subtraction angiography suggested the left adrenal gland. In February 1987, a benign phaeochromocytoma was uneventfully excised.

Some 2 years later the thymoma recurred and the patient died from myasthenia and septic shock following chemotherapy. There was no clinical evidence of recurrence of the phaeochromocytoma.

Discussion

Neuroendocrine malignancies are often multiple and are grouped under the various MEN syndromes. It is perhaps surprising that tumours of the thymus are not more frequently associated with other endocrine neoplasms. There have been isolated reports of thymoma associated with hyperparathyroidism[1] and MEN type I syndrome[2–4], but the author could find no previous reports of thymoma associated with phaeochromocytoma or MEN type II syndrome. This association was noticed during a review of the 34 thymomas resected at this unit over the past 10 years. Although the association of one phaeochromocytoma in this series may have been the result of chance, the occurrence of two such cases was rather striking and justified this report.

Carcinoid tumours are more commonly associated with MEN syndromes. In one review of the world literature[5] there were 65 such cases, although only 15 arose in the thymus. Thymoma and thymic carcinoid have occasionally been confused in the past, but in the two cases presented here the classical lymphocytic and epithelial elements of a true thymoma were seen.

Although it is difficult to make recommendations from two sporadic cases, it would seem sensible to suggest that all patients presenting with a phaeochromocytoma have their chest radiograph closely examined and that a detailed history of vasomotor symptoms be taken from those with thymoma.

Acknowledgements

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References

1. Palmer FJ, Sawyers TM. Hyperparathyroidism, chemodectoma thymoma and myasthenia gravis. *Arch Intern Med* 1978; **138**: 1402–3.
2. Schimke RN. Multiple endocrine adenomatosis syndromes. *Adv Intern Med* 1976; **21**: 249–65.
3. Rimoin DL, Schimke RN, eds. *Endocrine Pancreas: Genetic Disorders of the Endocrine Glands*. St Louis, Missouri: Mosby, 1971.
4. Vroegindeweij LJHM, Creemers GJM, Lockeseer JHM, Teepen JLJM. Myasthenia gravis and thymoma in multiple endocrine neoplasia (MEN I) syndrome. *J Neurol Neurosurg Psychiatry* 1990; **53**: 624–5.
5. Duh Q-Y, Hybarger CP, Geist R *et al.* Carcinoids associated with multiple endocrine neoplasia syndromes. *Am J Surg* 1987; **154**: 142–8.

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Vomiting caused by a dialysis fluid 'pseudocyst'

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The recognized mechanical complications of peritoneal dialysis include hernia, leakage, inadequate drainage, abdominal wall or scrotal oedema, pain, bleeding, intraperitoneal catheter loss, intestinal haematoma and perforation[1]. The previously unrecognized mechanical complication of vomiting secondary to dialysis fluid encysted within the lesser sac is reported.

Case report

In 1989 a 72-year-old woman with ischaemic heart disease was admitted for investigation of severe peripheral vascular disease. Some 20 years earlier she had suffered from bilateral tuberculous nephritis and undergone a right nephrectomy, which resulted in borderline renal failure. Renal function gradually deteriorated, and by 1983 continuous ambulatory peritoneal dialysis was required. Initially there were no problems with this treatment. Arterial investigations revealed reconstructable disease, so the patient underwent right femoropopliteal bypass grafting. After operation the woman developed persistent vomiting and could tolerate neither liquids nor solids. There was no abdominal pain or distension and no obvious cause could be found; the patient had normal haematology, stable biochemistry, no digoxin toxicity and had received no new medication. On the fourth day after operation a barium meal (*Figure 1*) showed the stomach to be stretched over a mass in the lesser sac; no other lesions were identified. Some 2 days later the patient suffered a cardiac arrest but received immediate successful cardiopulmonary resuscitation. The following day the vomiting had cleared and she could eat without difficulty; no further action was therefore taken. During the subsequent months dialysis was converted to haemodialysis because of difficulty with peritoneal dialysis at home. Almost 1 year after operation the patient was admitted to the renal ward with lethargy, loss of appetite and failure to cope at home. A barium meal showed that the mass in the region of the lesser sac was no longer present. The patient improved with continued haemodialysis and was discharged home.

Discussion

The lesser sac is a well recognized site for localized fluid collections. The causes include pancreatic pseudocyst and malignancy, posterior gastric ulcer perforation, cerebrospinal fluid[2] and haematoma[3]. Peritoneal dialysis fluid does find its way into the lesser sac, but distribution studies suggest that normally this site represents 1–3 per cent by volume[4]. In the present patient the stomach was stretched over an unusually large collection of dialysis fluid within the lesser sac. It is presumed that, as with pseudocysts, the pressure of the fluid on the stomach resulted in the continuous vomiting.

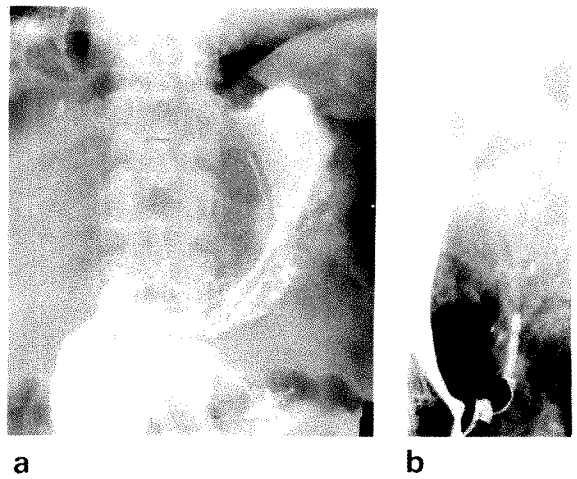

Figure 1 **a** *Anteroposterior and* **b** *lateral barium meal showing the stomach stretched anterolaterally over a fluid collection in the lesser sac*

It was interesting that during the period after arrest the patient had no vomiting. This resolution of symptoms could be explained if the forces exerted during cardiac massage had dispersed the fluid from the lesser sac. Because the patient had become asymptomatic no further assessment of the lesser sac was carried out until the second barium swallow on subsequent admission; this showed a normal gastric outline with no distortion.

This complication has not been previously reported. As large numbers of patients undergo continuous ambulatory peritoneal dialysis, it is a diagnosis to bear in mind in any case of unexplained vomiting.

References

1. Brenner BM, Rector FC. *The Kidney*. Vol. 2. 4th ed. Philadelphia, Pennsylvania: WB Saunders, 1991: 2318.
2. Agha FP, Amendola MA, Shirazi KK, Amendola BE, Chandler WF. Unusual abdominal complications of ventriculo-peritoneal shunts. *Radiology* 1983; **146**: 323–6.
3. Chambers SE, Best JJK, Ludlam CA. Lesser sac haematoma in a haemophiliac patient. *Br J Radiol* 1985; **58**: 474–5.
4. Twardowski ZJ, Tully RJ, Ersoy FF, Dedhia NM. Computerised tomography with and without intraperitoneal contrast for determination of intra-abdominal fluid distribution and diagnosis of complications in peritoneal dialysis patients. *ASAOI Trans* 1990; **36**: 95–103.

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Laparoscopic mobilization and exteriorization for minimally invasive small bowel resection

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The greatest effect of laparoscopy in operative surgery is in the rapid postoperative recovery of patients compared with that after laparotomy. This rapid recovery accrues from reduced injury to the abdominal wall with consequent reduction in postoperative pain and has led to the recent change from open to laparoscopic cholecystectomy[1]. Laparoscopic techniques are now being extended to other major abdominal operations[2-4].

New and complex instruments are being devised for intraperitoneal bowel anastomosis. However, in the majority of patients an abdominal wound will be needed to remove the resected specimen from the peritoneal cavity. As a result there may be no advantage to performing anastomosis within the abdominal cavity if the segment of intestine to be resected could be exteriorized through a similar incision. An approach to small bowel resection that combines the advantages of laparoscopy with those of open resection and anastomosis is described.

Surgical technique

In three patients diagnostic laparoscopy was performed through an incision below the umbilicus, using a 10-mm 0° telescope. The clinical details are given in *Table 1*. In two cases a barium study had shown a typical malignant stenosis and laparoscopy was performed to assess resectability, tumour invasion and distal metastases. In the third patient, laparoscopy was performed for acute abdominal pain and a large haemorrhagic jejunal diverticulum was found.

The lesions were freely mobile and were easily brought to the umbilicus using two accessory 5-mm laparoscopic cannulas and non-toothed grasping instruments. Although the primary tumours were mobile, patients 1 and 2 both had extensive nodal metastases that made curative resection impossible. A short midline incision was made by extending the infraumbilical incision to 3–5 cm, so as to exteriorize the segment of intestine. The blood supply was ligated and divided at the root of the mesentery, and the intestine was divided. End-to-end anastomosis was performed with a single layer of continuous absorbable polydioxanone sutures and the bowel was returned to the abdominal cavity.

Table 1 *Patient details*

Patient no.	Sex	Age (years)	Diagnosis
1	F	76	Mid-jejunal carcinoma
2	F	24	Mid-ileal carcinoma
3	F	32	Jejunal diverticulum

Operative time ranged from 60 to 90 min. Postoperative recovery was without complication. Patients were fully mobile on the day after surgery and were discharged from hospital 3–5 days later. Narcotic analgesia was not required; no postoperative paralytic ileus was seen. Histological examination confirmed adenocarcinoma with extensive lymph node involvement in two cases.

Discussion

This method of laparoscopic identification and mobilization of intestinal lesions allows a loop of intestine to be exteriorized through a small abdominal incision no bigger than that required to remove the primary tumour. It therefore affords the advantages of a laparoscopic operation (minimally invasive diagnosis and mobilization) while allowing a safe and easy anastomosis to be performed on the body surface. The operative time is similar to that required for full laparotomy and resection; specialized instruments may be advantageous but are not essential. The lesions were easily mobilized without any greater manipulation than at open operation. A similar technique has been used to remove an inflamed Meckel's diverticulum[5]. The advantage of less postoperative pain is evident subjectively. In addition, the adequacy of resection of locally invasive tumours and the success of laparoscopic lymph node dissection will need to be monitored when operation is performed with curative intent.

References

1. Grace PA, Quereshi A, Coleman J *et al.* Reduced postoperative hospitalization after laparoscopic cholecystectomy. *Br J Surg* 1991; **78**: 160–2.
2. Hill ADK, Attwood SEA, Murphy P, Stephens RB. Laparoscopic appendicectomy for acute appendicitis is safe and effective. *Ir J Med Sci* 1991; **160**: 268–70.
3. Mouret P, François Y, Vignal J, Barth X, Lombardi-Platet R. Laparoscopic treatment of perforated duodenal ulcer. *Br J Surg* 1990; **77**: 1006.
4. Nathanson LK, Shimi S, Cuschieri A. Laparoscopic ligamentum teres (round ligament) cardiopexy. *Br J Surg* 1991; **78**: 947–51.
5. Attwood SEA, Hill ADK, McGrath J, Stephens RB. Laparoscopic approach to Meckel's diverticulectomy. *Br J Surg* 1992; **79**: 211.

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226–229

Crohn's disease and anastomotic recurrence: microvascular ischaemia and anastomotic healing in an animal model

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Microvascular injury and ischaemia may be factors in anastomotic recurrence after resection for Crohn's disease. This hypothesis was explored in a ferret model of multifocal intestinal infarction. At laparotomy, isolated loops of small intestine were injected intra-arterially with styrene microspheres (test loop) or saline (control). At a second laparotomy 72 h later, test and control loops were divided and an end-to-end anastomosis performed between test loops ($n = 2$), test and control loops ($n = 9$) or control loops ($n = 2$). Abnormalities including chronic transmural inflammation, ulceration and granuloma formation were identified 2 weeks after the second operation in ten of the 11 surviving animals; changes were confined to the test loops and were most prominent adjacent to the anastomosis. No abnormalities were seen in control loops. The combination of two self-limiting ischaemic insults can produce a pattern of intestinal inflammation similar to that seen in anastomotic recurrence in Crohn's disease.

Recurrence at the anastomosis after surgical resection is a frequent and unexplained feature of Crohn's disease. Rutgeerts *et al.*[1,2] found endoscopic evidence of disease recurrence in over 70 per cent of patients within 1 year of surgery. Malchow *et al.* reported such recurrence in 82 per cent of patients by the third month after operation, suggesting this is an early event after surgical resection[3]. The creation of an anastomosis in patients with Crohn's disease may exacerbate this condition at the site of the anastomosis.

Multifocal granulomatous vasculitis has recently been demonstrated in segments of intestine affected by Crohn's disease[4,5]; the majority of granulomas in this condition arise as foci of vasculitis. These lesions may be present in any layer of the bowel wall but are located most frequently within the submucosal vascular plexus[5]. Their presence in macroscopically normal bowel suggests that they are early elements in the development of Crohn's disease[5–7]. Chronic intestinal ischaemia, as a consequence of these occlusive vascular lesions, might account for many of the features of the disease including ulceration, transmural inflammation and fibrosis.

In an attempt to explain the discontinuous distribution (skip lesions) of Crohn's disease, an animal model of multifocal gastrointestinal infarction has recently been developed[8]. This involves arterial embolization of ferret intestine with styrene microspheres of a diameter chosen specifically to occlude the submucosal microvascular plexus. A combination of 27- and 90-μm microspheres at a concentration of 20000–30000 microspheres per cm bowel produced acute transmural inflammation and mucosal ulceration at 24–48 h, but within 72 h the mucosa was regenerated[8].

The capacity of the intestine to heal after a localized devascularization, such as at an anastomosis, depends largely on the integrity of the submucosal plexus, which is the major collateral circulation within the bowel wall[9]. In Crohn's disease the submucosal plexus of macroscopically normal bowel is already compromised by vasculitis[4,5]. The additive effect of dividing the bowel, which may remove up to 50 per cent of the collateral circulation, may produce localized ischaemia sufficient to induce chronic inflammation. The present study explored this hypothesis in an animal model of submucosal microvascular occlusion[8].

Materials and methods

Home Office approval was obtained for all procedures. Female ferrets of mean weight 1 kg were used; the anaesthetic and laparotomy techniques have previously been described[8].

Initial procedure

At laparotomy, a combination of 27- and 90-μm diameter styrene microspheres (Sigma Chemicals, Poole, UK) at a concentration for each size of 10000–15000 microspheres per cm bowel length were injected intra-arterially into a suitable section of mid-gut (test loop) as previously described[8].

A second portion of bowel (control loop), two vascular arcades distal to the test loop, was used for a sham procedure in which isotonic saline without microspheres was injected. Test and control loops were marked with silk sutures in the mesentery. The abdomen was closed using a mass closure technique with Prolene (Ethicon, Edinburgh, UK) sutures. The skin was closed with interrupted silk sutures.

Secondary procedure

At 72 h, test and control animals appeared well and stool consistency and colour were normal. A second laparotomy was then performed, the timing being based on the observation of complete mucosal regeneration[8]. The test and control loops were reidentified and any macroscopic abnormalities noted.

In the first experiment (group 1; $n = 2$), test and control loops were divided at their mid-point and a full-thickness segment 0·2-cm long removed and placed in formalin for histological examination. The ends were then anastomosed (test loop to test loop, or control loop to control loop), a one-layer seromuscular anastomosis being performed using interrupted 8/0 Vicryl (Ethicon). In the second experiment (group 2; $n = 11$), the test and control loops were divided at their mid-point and the distal half of the former and proximal half of the latter removed in continuity and placed in formalin. An end-to-end anastomosis was then created between the test loop proximally and control loop distally.

To examine the 2-week morphological changes in intestine subjected to either intra-arterial microsphere embolization or anastomosis with no other surgical manipulation, two control animals (group 3) underwent intra-arterial injection of microspheres alone with no anastomosis and two (group 4) anastomosis alone without microsphere treatment.

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Terminal procedure

All animals were killed 2 weeks after the secondary procedure; terminal laparotomy was performed as previously described[8]. Serial tissue blocks were cut from test and control loops. In addition, single representative blocks were taken from the test loop 5 cm proximal to the anastomosis and areas of normal intestine proximal and distal to the anastomosis, well away from test and control loops. A minimum of 20 tissue blocks from each animal were paraffin-processed and sections from these stained with haematoxylin and eosin. All sections were coded and reviewed in a blind fashion.

Results

A total of 17 ferrets were studied. Two from group 2 died: one from unknown cause during the second laparotomy, and one 36 h after second laparotomy with an obstructed anastomosis (technical failure). Findings in the remaining 15 are described.

Secondary procedure

Macroscopic appearance. At 72 h all control loops appeared normal. There was a variable appearance of the test loops; eight looked normal or were slightly erythematous or oedematous, and the other three exhibited patchy inflammation and oedema with marked petechial haemorrhage in the adjacent mesentery (*Figure 1*). In these latter three animals division of the intestine before anastomosis was performed through an area with least macroscopic inflammation.

Microscopic appearance. All sections taken from test loops before anastomosis contained microspheres, except those from one animal in group 2. Microspheres were seen in the submucosa and occasionally within vessels in the lamina propria, and were surrounded by discrete aggregates of lymphocyte- and macrophage-like cells (*Figure 2*). In these sections there was no transmural inflammation or mucosal ulceration. Sections taken from the control loops before anastomosis showed no histological abnormality.

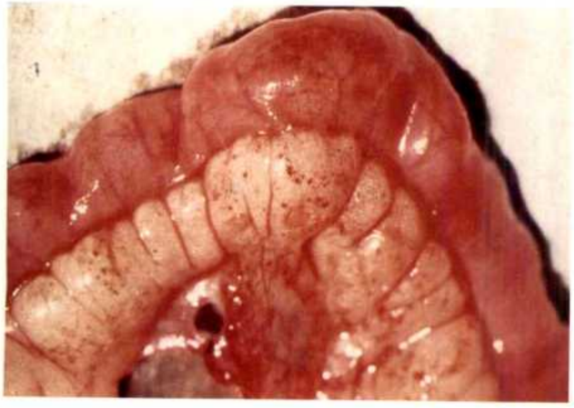

Figure 1 *Macroscopic appearance of test loop 72 h after injection of microspheres, showing patchy serosal inflammation*

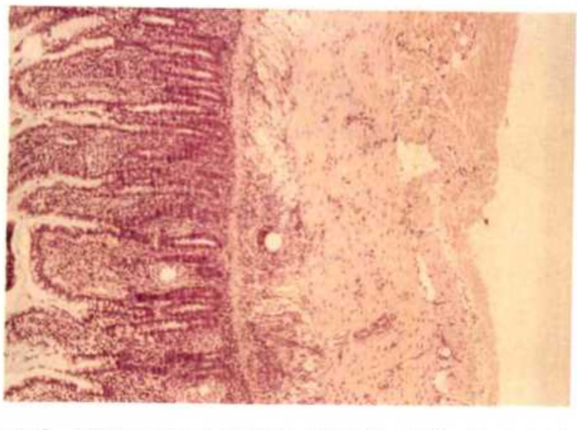

Figure 2 *Microscopic appearance of test loop 72 h after injection of microspheres, showing focal aggregates of chronic inflammatory cells around microspheres in the submucosa (centre field); the mucosa is intact. (Haematoxylin and eosin stain, original magnification ×50)*

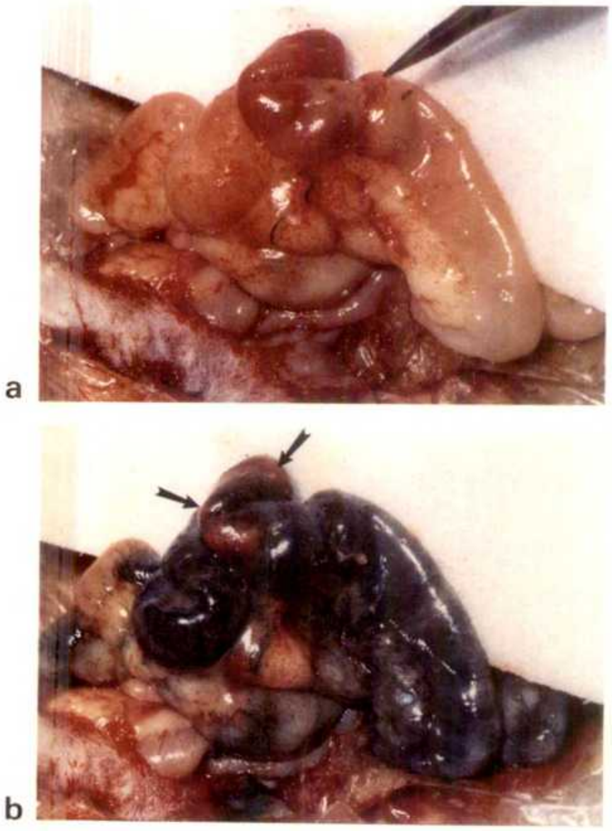

Figure 3 **a** *Macroscopic appearance of group 2 anastomosis 2 weeks after the secondary procedure. Test loop to the left of the anastomotic line (indicated by forceps) shows gross inflammation, in contrast to the normal appearance of the control loop to the right of the anastomosis.* **b** *Same specimen following perfusion with Indian ink. Normal perfusion of the control loop contrasts with patchy perfusion of the test loop with areas of underfilling (arrows)*

Terminal procedure

Macroscopic appearance. The only animals showing macroscopic changes at terminal laparotomy were three in group 2; these changes were confined to the test loops and consisted of mild serosal erythema, fibrinous adhesions or gross inflammation (*Figure 3a*). All anastomoses had healed. Test loops perfused with Indian ink exhibited a variable appearance; nine showed no perfusion defects and two patchy perfusion with areas of underfilling (*Figure 3b*). Control loops showed no perfusion defects when injected with Indian ink. In test and control anastomoses the ink, when perfusing preferentially one side of the anastomosis, did not cross the anastomotic line to perfuse the other side.

Microscopic appearance. A total of 401 sections were reviewed from the 15 animals with a minimum of 20 and maximum of 44 from each.

Sections taken from the four control anastomoses in groups 1 and 4 showed no histological abnormality (*Figure 4*) other than an occasional foreign-body granuloma associated with suture material. None of the nine animals in group 2 had evidence of inflammation on the control loop side of the anastomosis; there was no residual inflammation around microspheres in the two group 3 animals at 2 weeks.

The surgical procedures and microscopic findings in each group are summarized in *Figure 5*. Of the sections taken from group 1 ($n = 2$) and group 2 ($n = 9$) only one loop contained no microspheres or inflammation; this was possibly the result

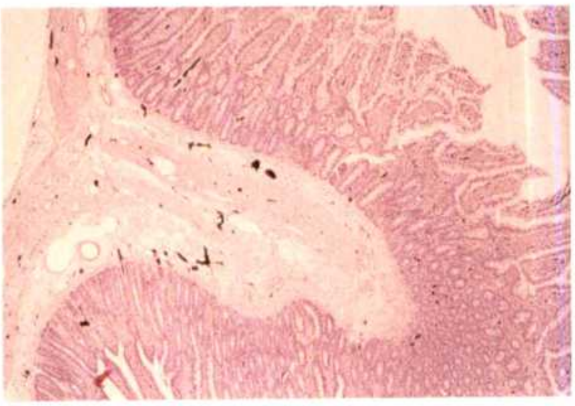

Figure 4 *Control anastomosis. Blood vessels of both the proximal and distal loops have filled with Indian ink. There is no mural inflammation. (Haematoxylin and eosin stain, original magnification × 50)*

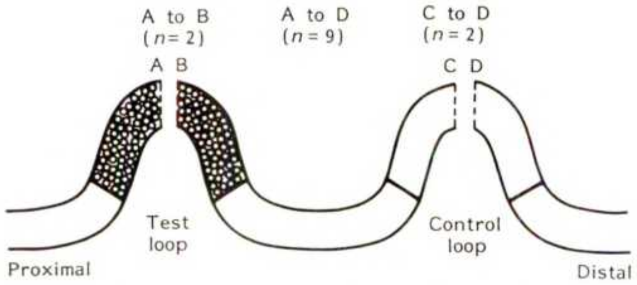

Figure 5 *Summary of operative procedures and histological findings in the 11 surviving animals in groups 1 and 2 at 2 weeks. A, B, C, D, anastomotic margin; ○, microsphere. Inflammation was observed at A and B in group 1 and at A in group 2. There was no inflammation at either C or D in group 1, or at D in group 2*

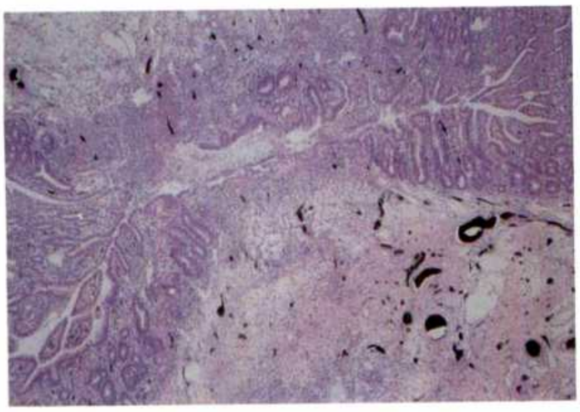

Figure 6 *Transverse section of a test loop of a group 2 animal 0·5 cm proximal to the anastomosis. Mucosa on diametrically opposed sides shows inflammation and ulceration. Transmural inflammation is seen in the centre and lower half of the field. (Haematoxylin and eosin stain, original magnification × 50)*

of an unrecognized technical error in the preparation of the microspheres. The other ten loops all had evidence of inflammation ranging from mucosal and/or submucosal (ten animals) to transmural (nine) (*Figure 6*) and frank ulceration (six) (*Figure 7*); inflammation was extensive, including granuloma formation, and associated with the presence of either suture material or microspheres (*Figure 8*). In four animals occasional submucosal granulomas were seen that had no apparent relationship to either suture material or microspheres in serial sections (*Figure 9*).

Inflammatory changes were consistently more severe in sections taken from tissue blocks adjacent to or within 1 cm of the anastomosis. These changes became progressively less severe in successive sections moving away from the anastomosis; in animals from group 1 they were seen in test loops on both sides of the anastomosis.

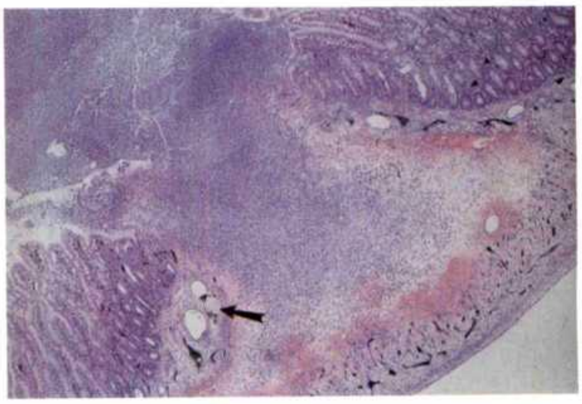

Figure 7 *Test loop of a group 2 animal adjacent to the anastomosis with ink-filled blood vessels. An intra-arterial microsphere is present (arrow). The centre field shows ulceration and inflammatory material; the ulcer base has penetrated almost the full thickness of the bowel wall. (Haematoxylin and eosin stain, original magnification × 50)*

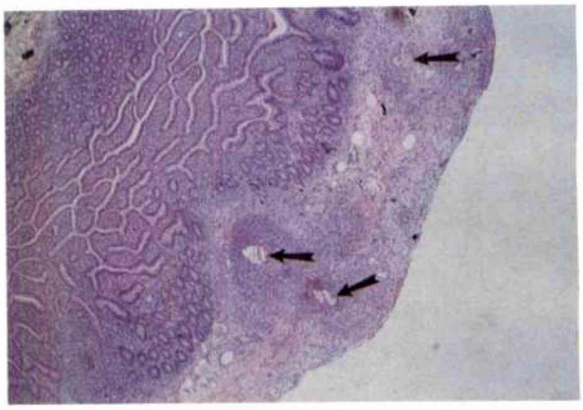

Figure 8 *Test loop of a group 2 animal adjacent to the anastomosis with occasional ink-filled blood vessels. Intense transmural inflammation can be seen, particularly around suture material (arrows). (Haematoxylin and eosin stain, original magnification × 50)*

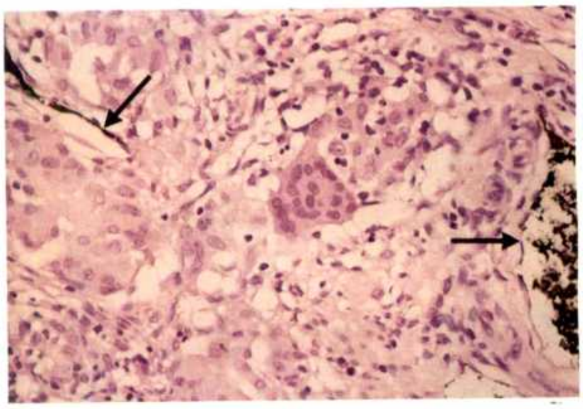

Figure 9 *Granuloma in the submucosa of a test loop of a group 1 animal. The granuloma is not related to either microspheres or suture material. The granuloma in the centre of the picture consists of histiocytes, a giant cell and lymphocytes; on either side are blood vessels (arrows) filled with ink. (Haematoxylin and eosin stain, original magnification × 1000)*

Discussion

The present study illustrates the critical role of the submucosal collateral plexus in the healing of an intestinal anastomosis. The model involves two acute vascular insults that on their own cause only transient damage to the intestinal mucosa with full healing after 2 weeks. The two insults together caused further ischaemia severe enough to produce obvious histological changes at 2 weeks but not to prevent healing of the anastomosis. The histological changes observed are similar to the chronic lesions characteristic of Crohn's disease. These include the relationship of histological inflammation to the anastomosis and its location on one or both sides of the anastomosis, depending on the original site of intestinal lesions before resection[10], the discontinuous and full-thickness distribution of the chronic inflammatory infiltrate, and mucosal ulceration.

The observation of isolated granulomas and intense granulomatous inflammation in relation to foreign material in the test loops suggests that chronic ischaemia may induce or propagate granulomatous inflammation. It is possible that foci of necrotic collagen caused by trauma or ischaemia could result in an inflammatory and granulomatous reaction, as has been proposed for Wegener's granulomatosis[11].

The anastomotic recurrence of Crohn's disease is usually proximal to the anastomosis, but there is a reduction in disease activity if the anastomosis is defunctioned[12]. An oedematous anastomosis produces narrowing of the intestinal lumen and intraluminal pressure rises proximal to an intestinal stricture[13], thus adding a third insult to the vascular supply at this site. Stricturoplasty may allow healing of diseased bowel by the relief of subacute obstruction with a consequent improvement of blood flow in the bowel wall. The present model is being used to investigate the relative roles of intraluminal pressure and luminal contents on microvascular ischaemia and associated inflammation.

The present study demonstrates that imposition of an anastomosis on an impaired submucosal collateral circulation leads to chronic inflammation of, and damage to, affected bowel. With a previous demonstration of granulomatous vasculitis and multifocal gastrointestinal infarction in Crohn's disease[4,5], the present study provides a possible explanation for the frequent localization of recurrent Crohn's disease at the site of surgical anastomosis.

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References

1. Rutgeerts P, Geboes K, Vantrappen G, Beyls J, Kerremans R, Hiele M. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990; **99**: 956–63.
2. Rutgeerts P, Geboes K, Vantrappen G, Kerremans R, Coenegrachts JL, Coremans G. Natural history of recurrent Crohn's disease at the ileocolonic anastomosis after curative surgery. *Gut* 1984; **25**: 665–72.
3. Malchow H, Weidmann B, Uhrberg G, Vestweber KH, Troidl H. The follow up of Crohn's disease – endoscopic diagnosis of early recurrence after surgery. *Proceedings of the Falk Symposium 60* 1990; **28**: 221–4.
4. Wakefield AJ, Sawyerr AM, Dhillon AP *et al.* Pathogenesis of Crohn's disease: multifocal gastrointestinal infarction. *Lancet* 1989; ii: 1057–62.
5. Wakefield AJ, Sankey EA, Dhillon DP *et al.* Granulomatous vasculitis in Crohn's disease. *Gastroenterology* 1991; **100**: 1279–87.
6. Morson BC. Crohn's disease. In: Brooke BB, ed. *Clinics in Gastroenterology.* London: WB Saunders, 1972: 265–77.
7. Hadfield G. The primary histological lesion of regional ileitis. *Lancet* 1939; ii: 773–5.
8. Hudson M, Piasecki C, Sankey EA *et al.* A ferret model of acute multifocal gastrointestinal infarction. *Gastroenterology* 1992; **102**: 1591–6.
9. Warwick R, Williams PL, eds. *Gray's Anatomy.* London: Longman, 1975: 1284–5.
10. Koch TR, Cave DR, Ford H, Kirsner JB. Crohn's ileitis and ileocolitis: a study of the anatomical distribution of recurrence. *Dig Dis Sci* 1981; **26**: 528–31.
11. Mark EJ, Matsutara O, Nehia S, Lin-Tan Fienberg R. The pulmonary biopsy in the early diagnosis of Wegener's (pathergic) granulomatosis. *Hum Pathol* 1988; **19**: 1065–71.
12. Rutgeerts P, Goboes K, Peeters M *et al.* Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. *Lancet* 1991; **338**: 771–4.
13. Morel P, Alexander-Williams J, Rohner A. Relation between flow–pressure–diameter studies in experimental stenosis of rabbit and human small bowel. *Gut* 1990; **31**: 875–8.

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Femoral hernia: intestinal obstruction is an unrecognized source of morbidity and mortality

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A total of 180 consecutive femoral hernia repairs, consisting of 100 emergency and 80 elective admissions between January 1979 and December 1986, were reviewed. Morbidity was greater in the emergency than in the elective group ($P < 0{\cdot}01$) *and was significantly related to intestinal obstruction* ($P < 0{\cdot}001$)*, a feature not previously highlighted. Intestinal obstruction also had an important association with mortality, which was confined to patients undergoing emergency surgery. Patients with intestinal obstruction are a high-risk group and require careful perioperative management. Wound infection predisposed to recurrence of femoral hernia* ($P < 0{\cdot}01$)*. Repair of recurrent hernia in patients treated electively was associated with an increased incidence of chest infection* ($P < 0{\cdot}001$)*. Prophylactic measures, including antibiotics, may help to reduce recurrence and its associated morbidity. Patients referred with an inguinal lump or hernia, as opposed to a femoral hernia, had a later outpatient appointment and consequently a later operation date* ($P < 0{\cdot}02$)*. All elderly patients referred with any groin lump should receive an early outpatient appointment.*

Femoral hernia repair may be associated with considerable morbidity and mortality[1]. Emergency surgery, advanced age, cardiorespiratory disease and delay in diagnosis contribute to mortality[1–3]. Morbidity has been analysed in a few series and is greater in patients presenting as an emergency[2]. This study of 180 consecutive femoral hernia repairs attempts to identify important factors affecting morbidity and mortality.

Patients and methods

All patients admitted between January 1979 and December 1986 with a diagnosis of femoral hernia were identified. The hospital notes up to December 1990 were reviewed. The study group consisted of 180 consecutive patients undergoing femoral hernia repair. Data were collected prospectively on a standardized pro forma. Referral modes and details, clinical presentation, investigations, operative details and postoperative course were recorded. Analysis of variables was made using the χ^2 test with Yates' correction.

Results

General features (Table 1)

The main points of difference between the elective and emergency groups were age >70 years ($P < 0{\cdot}001$) and associated cardiorespiratory disease ($P < 0{\cdot}01$).

Intestinal obstruction

Bowel obstruction was present in 39 per cent of patients undergoing emergency surgery, excluding one with carcinoma of the caecum and another with ascites from ovarian carcinoma. Those with obstruction differed from the group as a whole: the former had a less frequent history of a groin lump ($P < 0{\cdot}001$), an increased history of constipation ($P < 0{\cdot}01$) and frequently a preoperative serum urea level >8·0 mmol/l ($P < 0{\cdot}02$). On the other hand, patients who had bowel resected but did not have obstruction showed no significant difference in the distribution of clinical features except for delay in presentation >48 h ($P < 0{\cdot}01$). Delay in presentation was also characteristic of the group with obstruction ($P < 0{\cdot}001$) (*Table 2*).

Elective referrals

Letters of referral were traceable in 70 (88 per cent) of the elective group. A correct diagnosis of femoral hernia was made by the general practitioner in 28 patients (40 per cent). The majority of these (83 per cent) were seen within 4 weeks as opposed to 52 per cent of the remaining patients who were referred with an inaccurate diagnosis (21 as inguinal hernia, 14 as a non-specified groin lump, seven for miscellaneous reasons). Accuracy of diagnosis was improved by 37 per cent (26 patients) at the outpatient visit.

Table 1 *General features of the study groups*

	Elective surgery (n = 80)	Emergency surgery (n = 100)
Sex ratio (F:M)	59:21	77:23
Right:left*	49:28	76:20
Mean age (years)	54·5	74·7
>70 years (%)	31	68
Cardiorespiratory disease (%)	12	30
Groin lump for >1 year (%)	34	24
General anaesthesia (%)	91	90
Approach to hernia (low:high)	80:0	68:32
Mean hospital stay (days)	5·5	9·9

*Three hernias were bilateral in the elective group and four in the emergency group

Table 2 *Statistically significant features of patients with intestinal obstruction*

	Intestinal obstruction (n = 39)	Bowel resection without obstruction (n = 16)	Total for emergency group (%) (n=100)
History			
Groin lump	13 (33)	10 (62)	56
Recent constipation	22 (56)	5 (31)	39
Delay >48 h*	22 (56)	5 (31)	38
Urea level >8·0 mmol/l	20 (51)	4 (25)	35

Values in parentheses are percentages. *Mean delay for emergency group 3·2 days

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Table 3 *Complications of femoral hernia repair*

	Emergency surgery ($n = 100$)	Elective surgery ($n = 80$)	Total ($n = 180$)
Patients with complications	31 (31)	11 (14)	42 (23·3)
Complication			
Chest infection	10 (10)	4 (5)	14 (7·8)
Cardiac	9	0	9 (5·0)
Wound infection	7 (7)	2 (2)	9 (5·0)
Urinary infection	7 (7)	2 (2)	9 (5·0)
Renal failure	3	0	3 (1·7)
Deep vein thrombosis	2	0	2 (1·1)
Barry stricture	2	0	2 (1·1)
Adhesions	2	0	2 (1·1)
Recurrence of femoral hernia	1 (1)	4 (5)	5 (2·8)
Transient femoral paraesthesia	0 (0)	1 (1)	1 (0·56)
Total	43	13	56

Values in parentheses are percentages

Table 4 *Morbidity and mortality in the emergency subgroups*

Subgroup	Patients with obstruction	Morbidity	Mortality
Bowel resection ($n = 33$)	17	13 (10)	4 (2)
Viable bowel ($n = 30$)	18	11 (8)	2 (1)
Empty sac ($n = 15$)	2	3 (2)	0
Other ($n = 22$)	2	4 (2)	2 (1)
Total ($n = 100$)	39	31 (22)	8 (4)

Values in parentheses are patients with intestinal obstruction who developed complications or died

Mortality

Death was confined to patients undergoing emergency operation and the mortality rate was 4·4 per cent for the whole series. Age >70 years was associated with an increased mortality rate ($P < 0{\cdot}02$). Four of the eight patients who died had clinical intestinal obstruction; four had required bowel resection. The main causes of death were cardiac and respiratory. In two patients, both presenting with intestinal obstruction, the main mode of death was renal failure; advanced age (89 and 99 years) and late presentation were important contributory factors. Surgical approach did not affect the mortality rate significantly. However, a subgroup of nine patients, who initially had a low approach and subsequently required a high incision, had a higher mortality rate (22 per cent) compared with the remaining patients who had bowel resection (8 per cent).

Morbidity

Elective group. Morbidity was lower in the elective group ($P < 0{\cdot}01$). Eleven patients in that group developed complications (*Table 3*). Five of these had previous ipsilateral hernia repairs (two femoral, three inguinal); they accounted for all the four chest infections in the elective group. There were two wound infections; both were later complicated by recurrence of the femoral hernia.

Emergency group. Early and late complications occurred in 31 patients; multiple complications were present in eight of these (*Table 3*). Respiratory and cardiac causes accounted for 50 per cent of the early complications. Seven wound infections occurred in patients who underwent bowel resection, all of whom had clinical features of intestinal obstruction. Broad-spectrum antibiotics had been used. Three patients developed renal failure; two presented with intestinal obstruction. The most important clinical index of complications was the presence of intestinal obstruction ($P < 0{\cdot}001$). Bowel resection was also associated with a high incidence of postoperative complications, but this association was not statistically significant (*Tables 4* and *5*). The effect of surgical approach on morbidity was analysed in the high-risk group of patients with bowel in the hernia sac (*Table 6*). No significant difference was found between the high and low approaches. However, Barry stricture, an ischaemic stricture resulting from strangulation of the small bowel in a hernia[4], was a complication of the low approach in two cases.

Table 5 *Morbidity and mortality rates in emergency patients with obstruction and/or resection of bowel*

	Complication rate	Mortality rate
No obstruction		
No resection ($n = 45$)	6 (13)	2 (4)
Resection ($n = 16$)	3 (19)	2 (12)
Obstruction		
No resection ($n = 22$)	12 (55)	2 (9)
Resection ($n = 17$)	10 (59)	2 (12)
Total ($n = 100$)	31 (31)	8 (8)

Values in parentheses are percentages

Table 6 *Effect of surgical approach on morbidity and mortality in patients with bowel in the hernia sac*

	Low approach ($n = 26$)	High approach ($n = 28$)	Low with subsequent high approach ($n = 9$)
Age >70 years	19 (73)	22 (79)	6 (67)
Sex ratio (F:M)	20:6	20:8	6:3
Intestinal obstruction	15 (58)	15 (54)	5 (56)
Bowel resection	11 (42)	13 (46)	9 (100)
Morbidity (no. of patients)	9 (35)	11 (39)	4 (44)
Mortality	3 (12)	2 (7)	2 (22)

Values in parentheses are percentages

Recurrent femoral hernia

During the period 1979–1990 there were ten repairs of recurrent femoral hernia. Five patients underwent primary repair before 1979 and five in the period 1979–1986 (study group). Analysis of these recurrences showed 40 per cent with wound infection at the primary repair. This association was significant when recurrences in the study group were compared with those in the overall group ($P < 0{\cdot}01$).

Discussion

The bowel resection rate in the emergency group in this series was 33 per cent and the mortality rate 8 per cent, similar to that of other series with comparable resection rates[2]. However, despite the emphasis placed on the role of bowel resection[3,5], resection rate does not always reflect mortality rate (*Table 7*). Although intestinal obstruction may be a common form of presentation of emergency femoral hernia[9], its effect on mortality and morbidity has not previously been analysed. In this series 39 per cent of patients in the emergency group presented with intestinal obstruction. There was no significant difference in intestinal obstruction rate in patients with viable as opposed to resected bowel. Intestinal obstruction had an equally important association with mortality as bowel resection. The association with morbidity was highly significant for obstruction but not for bowel resection. Since two-thirds of patients with intestinal obstruction lacked a history of a groin lump and all had a palpable swelling, early diagnosis depends on examination of the groin. Delay in presentation

Table 7 *Literature reports of emergency femoral hernia repair*

Reference	Study period	Patients with emergency femoral hernia	Age (years)	Delay before presentation	Resection rate (%)	Obstruction rate	Total morbidity	Total operative mortality rate (%)	Mortality rate for bowel resection (%)
Waddington[6]	1965–1969	77	Mean 63 (range 30–90)	38·9% >2 days	20	—	—	1·4	—
Wheeler[7]	1963–1973	44	Range 19–86	—	22·7	—	23 (13 early, 10 late)	2·3	0
Blake and Lynn[1]	1969–1975	70	Mean 81·8 (range 75–97)	—	22·8	—	—	17·1	25
Andrews[3]	1974–1979	72	Range 0–100	—	18·0	—	—	15·0	—
Tasker[5]	1974–1980	38	Mean 65·1 (range 2–92)	Mean 4·28 days	31·6	—	26 early	15·8	41·6
Nicholson *et al.*[2]	1976–1980	63	68% >65 years	—	34·9	(58% with obstructive symptoms)	—	8·0	—
Brittenden *et al*[8]	1980–1990	44	Mean 72·9 (range 20–100)	Mean 1·4 days	9	—	13 early	5·0	—

causes uncorrected losses of fluid and electrolytes[3]. In the obstructed group, 56 per cent of patients presented 48 h after the onset of symptoms and 51 per cent had a serum urea level > 8·0 mmol/l. Abdominal distension resulting from obstruction causes further embarrassment in an elderly population with a high prevalence of cardiorespiratory disease. Adequate resuscitation and preparation for surgery without undue delay are necessary. Careful attention to perioperative fluid and electrolyte balance is important to prevent and counteract renal failure, an important contributor to morbidity and mortality in this series.

Mortality and morbidity rates were similar in comparable high-risk groups of patients undergoing a low or high approach to the hernia. A high approach has recently been reported to be associated with very low mortality and morbidity rates[8]. In the present series the low approach was disadvantaged by its association with two cases of Barry stricture, which did not occur with the high approach. This may be the result of better visualization and easier manipulation of the bowel in the latter approach, which the author recommends in emergency patients. Because of its lower incidence of recurrence the McEvedy approach[7] is favoured.

The femoral hernia recurrence rate of 2·8 per cent compares well with those of other studies[7]. Wound infection at the initial repair was an important aetiological factor. Careful long-term follow-up of infected hernia wounds should allow early detection and elective repair so as to avoid emergency repair of recurrence, which is associated with higher rates of bowel resection and mortality[3]. The high incidence of postoperative chest infection after repair of recurrence in the present series and the high risk of further recurrence[10] justify the prophylactic use of broad-spectrum antibiotics in this group of patients.

The low complication rate and zero mortality rate of patients treated electively support a policy of elective femoral hernia repair even in the elderly[11,12]. Furthermore, complications in the elective group increased mean hospital stay by only 1·7 days compared with 6·4 days in those treated as emergencies. Although the rate of correct diagnosis by general practitioners of 40 per cent compares well with that of other series[6], an improvement in diagnostic accuracy of 37 per cent could be achieved in the outpatient clinic. Early clinic appointment for all elderly patients referred electively with a groin lump or hernia is, therefore, recommended.

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References

1. Blake R, Lynn J. Emergency abdominal surgery in the aged. *Br J Surg* 1976; **63**: 956–60.
2. Nicholson S, Keane TE, Devlin HB. Femoral hernia: an avoidable source of surgical mortality. *Br J Surg* 1990; **77**: 307–8.
3. Andrews NJ. Presentation and outcome of strangulated external hernia in a district general hospital. *Br J Surg* 1981; **68**: 329–32.
4. Barry HC. Fibrous stricture of the small intestine following strangulated hernia. *Br J Surg* 1942; **30**: 64–9.
5. Tasker DG. Femoral hernia: a continuing source of avoidable mortality. *Br J Clin Pract* 1982; **36**: 141–4.
6. Waddington RT. Femoral hernia: a recent appraisal. *Br J Surg* 1971; **58**: 920–2.
7. Wheeler MH. Femoral hernia: analyses of the results of surgical treatment. *Proc R Soc Med* 1975; **68**: 177–8.
8. Brittenden J, Heys SD, Eremin O. Femoral hernia: mortality and morbidity following elective and emergency surgery. *J R Coll Surg Edinb* 1991; **36**: 86–8.
9. Cooke RV. Discussion on small bowel obstruction. *Proc R Soc Med* 1958; **51**: 505.
10. Bendavid R. Femoral hernias: primary *versus* recurrence. *Int Surg* 1989; **74**: 99–100.
11. Tingwald GR, Cooperman M. Inguinal and femoral hernia repair in geriatric patients. *Surg Gynecol Obstet* 1982; **154**: 705–6.
12. Allen PIM, Zager M, Goldman M. Elective repair of groin hernias in the elderly. *Br J Surg* 1987; **74**: 987.

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Comparative study of abdominal incision techniques

The characteristics of surgical incisions made with an electrosurgical technique were compared with those made using conventional methods in a prospective randomized trial. In particular, the claim that the method of incision may influence postoperative pain was investigated. A total of 101 consecutive patients receiving full-length midline laparotomy incisions for gastrointestinal resection were studied. A record was kept of the time required to make the incision and blood loss as well as postoperative pain (using a linear analogue scale), ventilatory function and requirement for analgesia. There were 50 patients in group 1 (scalpel; 15 men, 35 women) and 51 in group 2 (electrocautery; 26 men, 25 women). The groups were similar in age, body-weight, diagnosis and the type of surgical procedures being performed. Incision time was similar in the two groups but median blood loss during incision was significantly less in group 2 patients than in group 1 (10 versus *25 ml,* $P < 0.0001$*). Linear analogue pain scores were not significantly different between the groups at any stage after operation. The same was true of postoperative ventilatory function and requirement for analgesia. A total value for morphine use during the entire postoperative period was derived for each group and the median was 1·55 mg/kg for group 1 compared with 1·49 mg/kg for group 2. The electrosurgical method is associated with less blood loss during incision, although this study has failed to confirm any reduction in postoperative pain or requirement for analgesia in these patients.*

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In 1988 Hussain and Hussain[1] suggested that there was a significant difference in both subjective and objective measurements of pain in patients whose incisions were fashioned with an electrosurgical technique compared with those whose were made using a scalpel. That study was restricted to subcostal incisions for uncomplicated gallbladder surgery. In 1990 Dixon and Watkin[2] suggested that diathermy was quicker, gave better cosmetic results and resulted in no added discomfort to patients undergoing inguinal herniorrhaphy or cholecystectomy. Other studies have examined different properties of incisions in both skin[3,4] and intestine[5], comparing the use of various laser types, electrocautery and vibrating ultrasonic knives with that of conventional scalpels.

This study was designed to assess the electrosurgical technique in a wider range of abdominal surgery. An attempt was made to analyse whether there was any practical advantage to the surgeon, in terms of speed of incision and blood loss, in using cutting diathermy and any advantage to the patient in terms of ventilatory function, comfort and opiate requirements after surgery.

Patients and methods

Over an 18-month period, 101 consecutive patients under the care of one consultant (D.J.G.) undergoing laparotomy for any reason by means of a midline abdominal incision were invited to participate. Patients who on initial assessment had difficulty cooperating with the measurement techniques to be used in the postoperative period, and those who were unable to give informed consent, were excluded from the study.

Approval was obtained from the West Ethical Committee of Greater Glasgow Health Board. After obtaining written informed consent from each patient, baseline data were collected. It did not prove to be practical to standardize the drugs used for premedication and anaesthesia, for a variety of reasons. Patients were randomized by drawing an unmarked envelope in the operating room. Those in group 1 had a standard scalpel incision; in group 2 a scalpel was used simply to score the dermis and the remainder of the incision was made using an electrosurgical technique. All incisions were fashioned by a single operator and coagulation diathermy was used in both groups to control bleeding points. An Eschmann TD 411-S (Eschmann and Walsh, Lansing, UK) electrosurgical unit was used and was set to supply a pure cutting current (maximum power 400 W, usual setting 200 W) for cutting and a pinpoint coagulation current (maximum power 150 W, usual setting 75 W ± 15 per cent) for coagulation. The time taken to make the incision was recorded from the first skin incision until the peritoneum was open along the length of the wound and haemostasis had been achieved. Blood loss was measured by weighing of swabs using a standardized technique. Wound closure was standard throughout the study and consisted of a mass closure technique using a monofilament non-absorbable suture for the abdominal wall and a monofilament absorbable suture placed in the subcuticular layer for the skin.

An assessment of the postoperative pain score was made at 24, 48, 72 and 96 h after surgery using a 10-cm linear analogue scale. Postoperative peak expiratory flow rate (best of three readings) using a Wright's Mini Peak Flow Meter (Clement Clarke, Harrow, UK) was recorded at the same times after surgery. The measurements were not made within 2 h of the administration of any analgesic drugs and the values obtained were related to the preoperative performance.

Postoperative parenteral analgesia was available on demand. The amount of opiate analgesia administered in each 24-h period was calculated. A standard conversion factor was used as appropriate to convert non-morphine opiate doses into morphine equivalents[6]. All postoperative assessment was undertaken by an investigator unaware of the incision method used.

Groups were compared statistically by application of the Mann–Whitney *U* test or χ^2 test as appropriate.

Results

The two groups were similar in number of patients and basic characteristics such as age and body-weight (*Table 1*). The difference in sex ratio in the groups was significant (two-sample $\chi^2 = 3{\cdot}78$, 1 d.f., $P = 0{\cdot}05$). The groups were almost identical with regard to diagnosis and the type of surgical procedures

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Table 1 *Patient details*

	Group 1 (scalpel)	Group 2 (electrocautery)
Median age (years)	58 (38–66)	64 (54–71)
Median body-weight (kg)	60 (51·5–68)	66 (60–74)
Sex ratio (M:F)	15:35	26:25
Median incision time (min)	5 (5–8)	6 (4–6)

Values in parentheses are interquartile ranges

Table 2 *Linear analogue pain scores*

Time after operation (days)	Group 1 (scalpel)	Group 2 (electrocautery)
1	6 (4–8)	6 (5–7)
2	5 (3·5–6)	5 (3·75–7)
3	5 (4–6)	5 (3–6)
4	4 (2–5)	4 (3–5)

Values are median (interquartile range)

Table 3 *Peak expiratory flow rates*

	Peak expiratory flow rate (l/min)	
	Group 1 (scalpel)	Group 2 (electrocautery)
Before operation	385 (313–460)	399 (320–480)
Time after operation (days)		
1	217 (180–265)	218 (160–272)
2	220 (190–280)	237 (182–272)
3	260 (210–320)	272 (220–310)
4	282 (230–357)	293 (220–330)

Values are median (interquartile range)

Table 4 *Postoperative requirements for analgesia*

	Analgesia (mg morphine equivalent per 24 h)	
Time after operation (days)	Group 1 (scalpel)	Group 2 (electrocautery)
1	41·9 (28·1–50·0)	40·8 (27·5–50·0)
2	29·7 (20·0–37·5)	31·6 (22·5–40·0)
3	21·6 (11·9–25·1)	23·4 (12·5–37·5)
4	13·3 (0–17·4)	14·3 (0–20·0)

Values are median (interquartile range)

being performed. The majority (72 per cent) of patients underwent operation for colorectal cancer; the remainder had procedures to treat inflammatory bowel disease and a variety of other conditions.

The median times taken to make the incisions (5 min for group 1, 6 min for group 2) were not significantly different ($P = 0{\cdot}66$). Blood loss during incision was significantly different between the groups. In group 1 the median loss was 25 ml compared with 10 ml in group 2 ($P < 0{\cdot}0001$).

Linear analogue pain scores are shown in *Table 2*. There were no significant differences between the groups at any stage during the postoperative period. *Tables 3* and *4* show a summary of the results for postoperative ventilatory function and requirement for analgesia, respectively. Again, there were no significant differences between the groups. The median total value for morphine use during the entire postoperative period was 1·55 mg/kg for group 1 and 1·49 mg/kg for group 2. This difference was not statistically significant.

Discussion

The quantification of postoperative pain is notoriously difficult in view of the subjective nature of the assessment and the numerous variables that have been demonstrated to have a meaningful effect on the result.

One previous study[1] has suggested that the technique for making a surgical incision might have a direct effect on the subsequent discomfort suffered from the wound. If this observation could be substantiated there would be a clear opportunity for surgeons to improve the management of patients by adjusting their technique. The present study has failed to confirm that electrosurgically produced incisions are associated with less postoperative pain. The only difference between the two techniques was in blood loss from the skin and subcutaneous fat. This appears to be related to immediate coagulation of small vessels, in contrast to the oozing that occurs with a scalpel incision before coagulation ensues by activation of clotting factors.

The source of incisional pain is still a matter of considerable uncertainty. Attempts to influence pain fibres in specific layers of an abdominal wound by continuous infiltration of a local analgesic solution[7] or by transcutaneous electrical stimulation[8] have done little to advance understanding of the origin of incisional pain and the interplay of factors that may contribute to it. It may be that the results and conclusions of the present study differ from those obtained following subcostal incision because the midline abdominal wound is inherently more painful and any beneficial effect related to the incision technique may be overwhelmed by the severity of the discomfort.

It would seem most likely that a range of factors including characteristics of the incision have an influence on postoperative discomfort. The degree of abdominal distension, the duration of any paralytic ileus, the presence of inflammation or infection together with central and personality-related factors may all play an additional and important role in postoperative pain. There is no evidence to support the hypothesis that electrocautery reduces pain by the destruction of cutaneous nerve endings.

Some workers have suggested that the electrosurgical method is superior in that it is consistently quicker and gives better cosmetic results with minimal complications[2]. One group specifically compared the outcome in relation to septic wound complications and showed no difference between electrosurgical and conventional techniques[9]. It has been the experience of the present authors that the electrosurgical method is rapid, safe, convenient and haemostatic, and that no disadvantages are apparent. In particular, there were no problems with skin charring, burns, wound haematomas, infections or the complications of delayed healing or keloid formation in this study.

References

1. Hussain SA, Hussain S. Incisions with knife or diathermy and postoperative pain. *Br J Surg* 1988; **75**: 1179–80.
2. Dixon AR, Watkin DFL. Electrosurgical skin incision *versus* conventional scalpel: a prospective trial. *J R Coll Surg Edinb* 1990; **35**: 299–301.
3. Hambley R, Habda PA, Abeil E, Cohen BA, Jegasothy BV. Wound healing of skin incisions produced by ultrasonically vibrating knife, scalpel, electrosurgery and carbon dioxide laser. *J Dermatol Surg Oncol* 1988; **14**: 1213–17.
4. Pearlman LW, Steigmann GV, Vance V *et al.* A prospective study of incisional time, blood loss, pain and healing with carbon dioxide laser, scalpel and electrosurgery. *Arch Surg* 1991; **126**: 1018–20.
5. Puolakkainen P, Brackett K, Sankar MY, Joffe S, Schroder T. Effects of electrocautery, CO_2 laser and contact Nd:YAG laser scalpel on the healing of intestinal incision. *Lasers Surg Med* 1987; **7**: 507–11.
6. Medical Working Group on Drug Dependence. *Guidelines of good clinical practice in the treatment of drug misuse.* London: Department of Health and Social Security, 1984.

7. Gibbs P, Purushotham A, Auld C, Cuschieri RJ. Continuous wound perfusion with bupivacaine for postoperative wound pain. *Br J Surg* 1988; **75**: 923–4.
8. Galloway DJ, Boyle P, Burns HJ, Davidson PM, George WD. A clinical assessment of electroanalgesia following abdominal operations. *Surg Gynecol Obstet* 1984; **159**: 453–6.
9. Johnson CD, Serpell JW. Wound infection after abdominal incision with scalpel or diathermy. *Br J Surg* 1990; **77**: 626–7.

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Surgical workshop

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Sutureless laparoscopic treatment of perforated duodenal ulcer

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Perforated duodenal ulcer is amenable to laparoscopic treatment[1–4]. To date, laparoscopic surgeons have copied conventional techniques for this condition, but these can be technically demanding. A sutureless method for laparoscopic treatment of acute perforated duodenal ulcer using a gelatin sponge plug and fibrin sealant is presented. The procedure is quick, simple, secure and well suited to the laparoscopic environment.

Surgical technique

Pneumoperitoneum is established and the laparoscope is inserted via an infraumbilical incision. An 11-mm cannula is positioned in the epigastrium and a 5-mm cannula in the right upper quadrant. The perforation is usually in the anterior wall of the first part of the duodenum. If there is difficulty identifying it, moving the laparoscope to the epigastric port gives a good view of this area. Inserting the tips of a forceps into the perforation confirms its location.

A piece of gelatin sponge (Spongostan; Ferrosan, Soeborg, Denmark) approximately 20 × 15 mm is cut from a 10-mm thick sheet and rolled into a cylinder with one end compressed to produce a cone. This plug is grasped with a forceps and back-loaded into a 10-mm reducing sheath for insertion into the abdominal cavity. The plug is placed into the ulcer so that the base of the cone protrudes from the serosal surface. A 2-ml volume of two-component fibrin sealant (Tisseel; Immuno, Vienna, Austria) is slowly injected via a double-lumen catheter around the plug to secure it. Prewarming of the sealant facilitates rapid reaction. A fold of omentum may be laid over the plug but this is not fixed in place. Peritoneal lavage is performed with 2 litres warm saline before completion of the operation.

Nasogastric drainage is maintained for 1–2 days after operation before reintroduction of diet. A course of intravenous antibiotics and histamine antagonist is prescribed.

Discussion

Laparoscopic treatment of a perforated duodenal ulcer avoids the need for a large incision without preventing adequate peritoneal toilet. Postoperative morbidity rates are likely to be reduced, although no randomized study has yet been published. A sutured omental patch is effective, but laparoscopic suturing is technically difficult both in the accurate placement of sutures and knot tying. The procedure takes longer than open operation and needs to be performed by a surgeon experienced in laparoscopic procedures.

The gelatin sponge plug technique offers a quick, simple and secure method for laparoscopic treatment of perforated duodenal ulcer. Potentially, it is of value in any such case and could be performed readily by surgeons with basic training in laparoscopic surgery. An immediate and effective seal of the perforation is achieved. The size of the plug can be tailored to suit individual cases; a relatively large ulcer is not a contraindication.

The cost of the small volume of fibrin sealant is reasonable. Special endoscopic double-lumen catheters may be obtained from the manufacturer, or a central venous catheter can be employed after cutting off the tip. Rarely, there may be allergic reaction to the fibrin sealant.

References

1. Mouret P, François Y, Vignal J, Barth X, Lombard-Platet R. Laparoscopic treatment of perforated peptic ulcer. *Br J Surg* 1990; **77**: 1006.
2. Nathanson LK, Easter DW, Cuschieri A. Laparoscopic repair/peritoneal toilet of perforated duodenal ulcer. *Surg Endosc* 1990; **4**: 232–3.
3. Fletcher DR, Jones RM. Perforated peptic ulcer. A further application of laparoscopic surgery. *Aust N Z J Surg* 1992; **62**: 323–4.
4. Sunderland GT, Chisholm EM, Lau WY, Chung SCS, Li AKC. Laparoscopic repair of perforated peptic ulcer. *Br J Surg* 1992; **79**: 785.

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Surgical workshop

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Laparoscopic truncal vagotomy without drainage

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The scope of laparoscopic surgery is rapidly expanding. A technique of laparoscopic truncal vagotomy without drainage for the treatment of chronic duodenal ulcer is described. The rationale for this procedure, initial technique and clinical outcome have previously been reported[1].

Surgical technique

The patient is placed supine on the operating table. After induction of general anaesthesia, a wide-bore orogastric tube is passed. With the patient in a 20° head-up position, pneumoperitoneum is established with carbon dioxide via a Veress needle placed in the right upper quadrant at the mid-clavicular line 1 cm below the costal margin. A 10-mm SurgiPort (US Surgical, Norwalk, Connecticut, USA) with a sleeve length of 15 cm is introduced at the Veress puncture site (port 1) (*Figure 1*). A 0° 10-mm laparoscope is introduced through this cannula and the contents of the peritoneal cavity inspected. Two further 10-cm long 10-mm diameter cannulas are inserted (ports 2 and 3). The 0° laparoscope is replaced by a 25° oblique 10-mm laparoscope introduced through the subumbilical cannula. Another 10-cm long 10-mm diameter cannula is inserted at port 4. A 10-mm grasping forceps is introduced at port 1 and used to direct the shaft of this long SurgiPort inferior to the falciform ligament and then superiorly along the under-surface of the left lobe of the liver towards the oesophageal hiatus. The left lobe is then raised, using the shaft of the SurgiPort, until the site of the intra-abdominal oesophagus is exposed. A 10-mm grasping forceps is inserted through a cannula at port 3, and the closed forceps is placed at the angle of His and used to retract the stomach downwards, putting the intra-abdominal oesophagus under tension. The phreno-oesophageal ligament is dissected upwards using a 5-mm dissecting forceps at port 4. The peritoneum over the anterior surface of the oesophagus is opened and gently dissected downwards with careful haemostasis. The whole of the anterior wall of the intra-abdominal oesophagus is thus exposed. The anterior vagus nerve is identified, dissected free of the oesophagus and held with the forceps at port 4. The trunk is cauterized and divided by scissors introduced through a cannula at port 3. Any remaining strands of the anterior vagus on the oesophagus are cauterized and divided. The 10-mm grasping forceps at port 3 is placed to the right of the oesophagus and used to displace the latter to the left. The posterior vagus is identified on the right crus of the diaphragm to the right of the displaced oesophagus. It is then divided in a similar manner to the anterior vagus nerve. After haemostasis is assured the cannulas are removed. The orogastric tube is replaced by a nasogastric tube. The latter is removed and oral fluids commenced on day 1 after operation; a normal diet is tolerated from day 2.

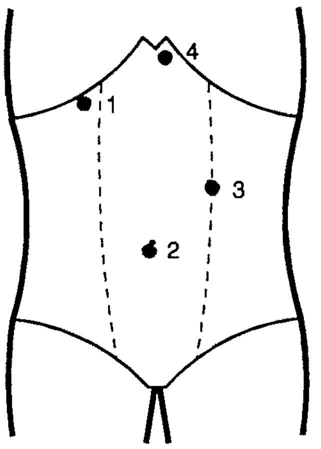

Figure 1 *Sites of ports: 1, right upper quadrant, mid-clavicular line 1 cm below the costal margin; 2, subumbilical; 3, 6 cm above the umbilicus in the mid-clavicular line; 4, 1 cm to the left of the midline, 1 cm below the angle between the xiphisternum and left costal margin*

Discussion

This paper describes the use of a 10-mm SurgiPort with a 15-cm long sleeve to raise the left lobe of the liver. This has been found easier and safer to use than the fan retractors currently available. The other technical difficulty in this procedure is achievement of adequate inferior traction on the intra-abdominal oesophagus. This manoeuvre facilitates identification of the anterior vagal trunks. Attempts have been made to achieve this traction by the intraoperative introduction of a gastroscope or wide-bore orogastric tube. The latter was found to be simpler to use and equally effective. Undoubtedly, the development of appropriate instruments to grasp and retract the gastric cardia safely will make this manoeuvre easier. Access to the posterior vagus can also be achieved by dividing the lesser omentum with transection of the hepatic branch of the anterior vagus nerve. It has been found that this is not always necessary.

Laparoscopic posterior truncal vagotomy with lesser curve anterior gastric myotomy has been described for the management of chronic duodenal ulcer[2]. However, this technique is much more difficult than that described here. The introduction of H_2-receptor antagonists in the management of chronic duodenal ulcer may have resulted in too few patients being submitted to surgery. If this new procedure proves to be as safe and effective as open truncal vagotomy and pyloric dilatation, a more rational balance between early operation and prolonged drug therapy may be struck[3,4].

References

1. Murphy JJ, McDermott EWM. Laparoscopic truncal vagotomy without drainage for the treatment of chronic duodenal ulceration. *Ir Med J* 1991; **84**: 125–6.
2. Kathouda N, Mouiel J. A new technique of surgical treatment of chronic duodenal ulcer without laparotomy by videocelioscopy. *Am J Surg* 1991; **161**: 361–4.
3. Thompson JD, Galloway JB. Vagotomy and pyloric dilatation in chronic duodenal ulceration. *BMJ* 1979; **i**: 1453–5.
4. Pringle R, Irving AD, Longrigg JN, Wisebey M. Randomized trial of truncal vagotomy with either pyloroplasty or pyloric dilatation in the surgical management of chronic duodenal ulcer. *Br J Surg* 1983; **70**: 482–4.

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Single-loop biliary and gastric bypass for irresectable pancreatic carcinoma

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Twenty-five patients with irresectable carcinoma of the pancreatic head received a modified type of palliative bypass in which the transected bile duct and the gastric antrum were anastomosed to the same Roux loop of jejunum. There were 13 women and 12 men with a median age of 54 (range 35–74) years. All but three patients were jaundiced and 11 underwent preoperative biliary decompression. In 18 patients jaundiced at the time of operation, the median preoperative serum bilirubin level was 287 (range 57–804) µmol/l. The median operative time was 4·0 (range 2·5–6·0) h. There were no hospital deaths. Minor postoperative complications occurred in nine patients and the median hospital stay after operation was 13 (range 7–49) days. The median postoperative survival was 4·8 (range 1·5–11·5) months. This operation provides good palliation safely in selected patients with irresectable pancreatic carcinoma.

Approximately 15 per cent of pancreatic cancers are resectable but few patients are cured[1]. For those with irresectable tumours presenting with obstructive jaundice, non-operative stenting or surgical bypass are the two treatment options. In reasonably fit patients (without cachexia or ascites) an operative approach may be preferred, allowing confirmation of the nature and irresectability of the tumour, plus relief of jaundice, vomiting and pain. The use of the gallbladder or duodenum for bypass is attended by poor results[1]. A new technique involving a retrocolic Roux loop for anastomosis to the bile duct and gastric antrum has been used for the past 6 years.

Patients and methods

Patients

The single-loop biliary and gastric bypass procedure was carried out in a consecutive series of 25 patients with irresectable carcinoma of the pancreatic head between 1985 and 1991. There were 13 women and 12 men with a median age of 54 (range 35–74) years. All had histological confirmation of pancreatic ductal carcinoma. Each operation was performed by one of the authors (R.C.N.W.) or his senior registrar.

To set this experience in context, during the same period 24 pancreatoduodenectomies were carried out for ductal carcinoma of the pancreatic head. Several patients received endoscopic or percutaneous stenting, but others were probably not referred because of the advanced nature of the disease. There were no patients whose cancer was so extensive at laparotomy that bypass could not be performed.

Clinical and operative details were prospectively recorded. Follow-up was obtained from the last recorded clinic attendance and from telephone or postal contact with the patient, relatives or general practitioner.

Operative technique

Laparotomy was carried out initially through a right subcostal incision. In the absence of hepatic or peritoneal metastases, the incision was extended to the left and a trial dissection was undertaken to assess resectability. Visceral angiography was used in those with a potentially resectable tumour[2]. The relationship of the tumour to the portal vein and its posterior fixity were checked at operation. If a preoperative biopsy was not available, a tissue specimen was obtained from a convenient metastasis or by direct (not transduodenal) biopsy of the primary tumour using a Tru-Cut needle (Travenol Laboratories, Thetford, UK). The specimen was sent for frozen section, and further biopsies were performed until a positive diagnosis of carcinoma was obtained.

The bypass involved anastomosis of the common hepatic duct and gastric antrum to the same retrocolic Roux loop of jejunum (*Figure 1*). The gallbladder was removed to improve access. The bile duct was mobilized and transected above the entry of the cystic duct and at least 2 cm above the 'leading edge' of the tumour; the lower bile duct was oversewn. A 40–50-cm retrocolic Roux loop was created to the right of the middle colic vessels. The top of the loop was closed and invaginated, and the following anastomoses were created: (1) end-to-side hepaticojejunostomy in one layer of absorbable 3/0 Vicryl sutures (Ethicon, Edinburgh, UK). The biliary anastomosis was fashioned 10–15 cm below the top of the Roux loop; (2) side-to-side gastrojejunostomy just below the apex of the Roux loop using a two-layer anastomosis; and (3) enteroanastomosis in two layers.

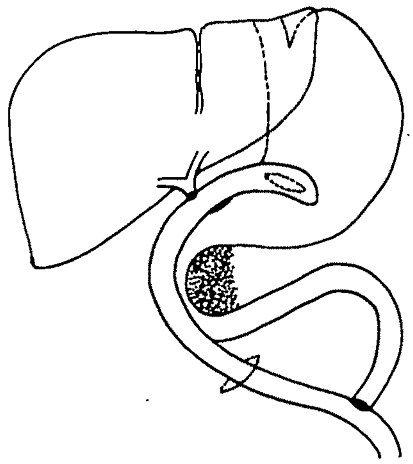

Figure 1 *Single-loop biliary and gastric bypass procedure for irresectable pancreatic carcinoma*

Results

Presenting features (Table 1)

The three non-icteric patients had the lesion demonstrated by ultrasonography and/or computed tomography (CT) and presented with acute pancreatitis (one patient) and abdominal pain (two). In four patients jaundice had been completely relieved by preliminary decompression of the biliary tree. The median serum bilirubin level in the other 18 patients was 287 (range 57–804) µmol/l. Median weight loss in 17 patients was 6·5 (range 2–19) kg, and half the patients had troublesome epigastric and/or back pain. Of six patients with vomiting, only

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Table 1 *Clinical features of 25 patients with irresectable pancreatic carcinoma*

Clinical presentation	No. of patients	Median (range) duration (weeks)
Symptoms		
Jaundice	22	3 (0·5–16)
Weight loss	17	6 (2–24)
Abdominal and/or back pain	13	5 (3–16)
Vomiting	6	7 (2–12)
Steatorrhoea	1	8
Signs		
Palpable gallbladder	10	
Hepatomegaly	2	
Epigastric mass	1	
Ascites	1	

Table 2 *Contraindications to pancreatic resection in 25 patients with cancer*

	No. of patients
Vascular involvement	15
Multiple liver metastases	9
Multiple lymph node metastases	6
Extensive involvement of mesenteric root or mesocolon	3
Multiple peritoneal seedings	2

Table 3 *Postoperative complications in nine patients*

	No. of patients
Delayed gastric emptying	3
Biliary fistula	2
Intra-abdominal collection	2
Transient gastrointestinal bleeding	1
Other (pleural effusion, atelectasis, deep vein thrombosis)	3

three had duodenal invasion (including one with early gastric outlet obstruction).

Preoperative imaging

Ultrasonography demonstrated the primary tumour in 17 of 23 patients but detected liver metastases in only four of nine. CT showed the primary in 17 of 18 patients and liver secondaries in three of five. Cholangiography was performed in 19 patients by the endoscopic retrograde route (16) and/or percutaneous transhepatic route (eight). Visceral angiography suggested irresectability in 13 of 20 patients: portal vein involvement (ten), arterial encasement (six) and/or liver metastases (one). Five patients had a percutaneous biopsy and in a sixth a tissue diagnosis was obtained at previous operation.

The bile duct was decompressed before operation in 11 patients, by endoscopic retrograde cholangiography in four, percutaneous transhepatic cholangiography (PTC) in four and at a preliminary operation in three. In only four of these did the serum bilirubin level return to normal before operation. Although some patients were referred with indwelling stents, preoperative biliary decompression was avoided if the tumour was clearly irresectable.

Operative assessment

Major vascular involvement was the most common reason for irresectability (*Table 2*); angiography intimated this in 12 of the 15 patients. Metastatic spread otherwise precluded resection more often than direct tumour extension. Peroperative biopsies were obtained from the primary tumour (12), liver deposits (nine) or lymph nodes (three). Despite multiple biopsies the diagnosis of carcinoma could not be confirmed in one patient who died 3 months after operation; autopsy revealed carcinomatosis from cancer of the pancreatic head.

Operation time varied from 2·5 to 6·0 (median 4·0) h, depending largely on the extent of the trial dissection needed to confirm irresectability. Chemical splanchnicectomy was performed in four patients.

Postoperative course

There were no deaths within 30 days and all patients left hospital. The median postoperative hospital stay was 13 (range 7–49) days. The serum bilirubin level had fallen by half in 18 patients within 2 weeks and was normal in ten of these. Jaundice was eventually relieved in every case.

Postoperative complications are shown in *Table 3*. A biliary fistula occurred in two patients, one from the site of previous PTC drainage and one from the choledochojejunostomy. In each patient the fistula dried up quickly after temporary percutaneous stenting. Two patients developed an intra-abdominal collection requiring percutaneous drainage, and one of these collections contributed to the long hospital stay of 49 days.

Outcome

The median postoperative survival was 4·8 (range 1·5–11·5) months. Twelve patients had adjuvant radiotherapy or chemotherapy, with combined treatment in eight of these. Four patients remain alive at 4, 4, 6 and 8 months after operation. Two patients with multiple liver metastases developed recurrent jaundice shortly before death. Gastric outlet obstruction did not occur. There was no instance of bile vomiting or cholangitis, and no patient required reoperation or readmission to hospital until the terminal stages of disease.

Discussion

Despite the availability of percutaneous or endoscopic methods for relieving jaundice, surgical bypass remains a valid alternative since there were no deaths and no reoperations. Advantages are twofold. First, operation establishes the diagnosis of cancer and confirms irresectability. Percutaneous biopsy is fallible[3,4]. Venous-phase angiography and CT are helpful in determining major vascular involvement but cannot always differentiate between compression and invasion of the portal vein[5]. Second, operation facilitates long-term relief of jaundice without the need for repeat endoscopy; it circumvents duodenal obstruction (present or future) and palliates pain. To justify an operative policy in patients with a very limited life expectancy, it is necessary that these objectives be achieved reliably and with a short hospital stay.

Like many others, the authors prefer to use the common hepatic duct rather than the gallbladder for bypass. The rationale of dividing the bile duct above the tumour is to prevent upwards extension of carcinoma in the duct wall or periductal tissues and thereby 'protect' the choledochojejunostomy. Although median survival was short (4·8 months), there were no episodes of cholangitis and no further jaundice (except in those with massive hepatic replacement), suggesting that the biliary anastomosis functioned satisfactorily.

Since 13–34 per cent of patients with pancreatic cancer receiving biliary diversion alone will develop duodenal obstruction before death, and since concomitant gastric bypass does not statistically increase the operative risk[1], prophylactic gastroenterostomy is carried out in those with an expectation of life beyond 1–2 months. The modified bypass used in the present series introduces food at the top of the defunctioned jejunal loop and should minimize reflux bile gastritis. Only one patient with an advanced cancer had a postoperative bleed and there was no bile vomiting. Upper gastrointestinal haemorrhage occurs in up to 17 per cent of patients with double bypass[6–10], but acid-reducing drugs may have had an additional protective effect. To be certain of preventing bile reflux, the biliary and gastric anastomoses would need separation by some 50 cm, or a separate Roux loop would be required. This study shows that these expedients are unnecessary.

Paradoxically, 20 per cent of patients (range 6–29 per cent in collected series)[1] will develop delayed gastric emptying after duodenal bypass, perhaps because of autovagotomy in those with extensive coeliac nodes. The incidence of delayed emptying in this series was low (12 per cent) and all patients were eating within 2 weeks. This finding accords with the observation of Jacobs *et al.*, who reported that 17 per cent of patients with a gastrojejunostomy proximal to the biliary anastomosis developed delayed gastric emptying, as opposed to 27 per cent of those with the reverse pattern[9]. Since no patient developed late gastric outlet obstruction, the theoretical risk of tumour encroachment on the mesocolic window should not preclude the convenient use of a retrocolic Roux loop.

Quality of life is difficult to assess in a group of patients, half of whom received adjuvant oncological therapy. Generally pain was well controlled and jaundice did not recur. The absence of late obstructive complications requiring readmission to hospital and the certainty that a resectable tumour had not been overlooked were the main justifications for an operative approach to pancreatic cancer. The single-loop biliary and gastric bypass procedure has worked well in practice and should be considered for those with irresectable cancer and a reasonable expectation of life.

References

1. Watanapa P, Williamson RCN. Surgical palliation for pancreatic cancer: developments during the past two decades. *Br J Surg* 1992; **79**: 8–20.
2. Appleton GVN, Bathurst NCG, Virjee J, Cooper MJ, Williamson RCN. The value of angiography in the surgical management of pancreatic disease. *Ann R Coll Surg Engl* 1989; **71**: 92–6.
3. Dickey JE, Haaga JR, Stellato TA, Schultz CL, Hau T. Evaluation of computed tomography guided percutaneous biopsy of the pancreas. *Surg Gynecol Obstet* 1986; **163**: 497–503.
4. Taavitsainen M, Koivuniemi A, Bondestam S, Kivisaari L, Tierala E. Ultrasonically guided fine-needle aspiration biopsy in focal pancreatic lesions. *Acta Radiol* 1987; **28**: 541–3.
5. Trede M. The surgical treatment of pancreatic carcinoma. *Surgery* 1985; **97**: 28–35.
6. Richard AB, Sosin H. Cancer of the pancreas: the value of radical and palliative surgery. *Ann Surg* 1973; **177**: 325–31.
7. Schantz SP, Schickler W, Evans TK, Coffey RJ. Palliative gastroenterostomy for pancreatic cancer. *Am J Surg* 1984; **147**: 793–6.
8. Kairaluoma MI, Kiviniemi H, Laitinen S, Ståhlberg M. Staplers in palliative bypass surgery for unresectable pancreatic cancer. *Pancreas* 1987; **2**: 146–51.
9. Jacobs PPM, van der Sluis, Wobbes T. Role of gastroenterostomy in the palliative surgical treatment of pancreatic cancer. *J Surg Oncol* 1989; **42**: 145–9.
10. Blievernicht SW, Niefeld JP, Terz JJ, Lawrence W Jr. The role of prophylactic gastrojejunostomy for unresectable periampullary carcinoma. *Surg Gynecol Obstet* 1980; **151**: 794–6.

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Porcine islet isolation: prospective comparison of automated and manual methods of pancreatic collagenase digestion

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A prospective study was undertaken to compare an automated method of porcine pancreatic digestion with a simpler manual procedure. These techniques have not previously been compared directly. After intraductal distension with collagenase, seven porcine pancreata were divided longitudinally; half of each was digested by the automated method and half by the manual technique. Islet yield and purity were measured. Compared with the manual technique, the automated method isolated a significantly greater total volume of islet tissue (median (range) 3·56 (1·39–5·30) versus *1·07 (0·46–1·92) mm^3/g,* P = *0·022), increased the median (range) number of 105-μm islet equivalents isolated (5875 (2294–8746)* versus *1766 (759–3168) per g,* P = *0·022) and improved the islet cleavage index (median (range) 92 (89–99)* versus *82 (78–92) per cent,* P = *0·035). It is concluded that, although the automated method is more complicated to set up, it greatly improves the yield of intact islets from the porcine pancreas.*

The isolation of large numbers of viable islets of Langerhans from the pancreas is a prerequisite for successful islet transplantation. Efficient isolation depends on the dissociation of the pancreas into its separate components and is usually accomplished by enzymatic collagenase digestion of the fibrous stroma followed by mechanical dispersion of the digested tissue[1]. The subsequent purification of islets from contaminating acinar tissue is usually achieved by density-gradient centrifugation and is critically dependent on the efficiency of the initial digestion process. Although the delivery of collagenase by the intraductal route is now a standard technique for the enzymatic digestion of pancreata from humans and large animals[2], many methods of mechanical dispersion have been employed, including manual shaking, teasing with forceps[2,3], mincing or maceration[4–6] and trituration[7–9]. The most effective procedures, however, depend on minimal mechanical trauma to the islets and their immediate removal, once liberated, from the injurious effects of collagenase. Although two recently described techniques[3,10] fulfil these criteria and have been reported to produce similar results in the human, they have not yet been compared directly. The purpose of this prospective study was therefore to compare the results of porcine pancreatic collagenase digestion, using the automated method described by Ricordi *et al.*[10], with those of the manual biopsy-based technique of London *et al.*[3].

Materials and methods

Pancreas procurement

Porcine pancreata were obtained from a local abbatoir, with a median warm ischaemia time of 7 (range 5–9) min. Donor pigs were of Large White–Welsh crossbreed, 6–8 months old, in the weight range 80–100 kg. The splenic lobe of the pancreas was removed and transported to the laboratory in cold (4°C) hyperosmolar citrate solution (Travenol Laboratories, Thetford, UK). In the laboratory, the gland was cleaned of fat and lymphoid tissue, weighed, and the main pancreatic duct cannulated with a 3-Fr catheter (Portex, Hythe, UK) which was ligated in place.

The pancreas was warmed for 2 min in minimum essential medium (MEM) at 35°C and then distended (2 ml per g pancreas) by injection into the cannula of Hanks' balanced salt solution containing 2 mg/ml collagenase (Collagenase Pan Plus; Serva, Heidelberg, Germany) and 0·02 mg/ml DNAse (Sigma Chemicals, Poole, UK). Uniform distension was obtained by gradual withdrawal of the cannula during injection. The distended pancreas was reweighed, sectioned longitudinally along the line of the main pancreatic duct, and the weight of each portion recorded. One half of each gland was then digested by the manual method and the other half by the automated procedure. Digestions were performed simultaneously by two teams.

Manual digestion

A biopsy was taken from the region of the pancreas that was seen to distend first, usually the tail, and divided into five pieces. Each piece was incubated at 35°C in a universal container with 1 ml prewarmed dithizone (Sigma; 1·2 mmol/l in 5 per cent (v/v) dimethyl sulphoxide–MEM and 1 per cent bovine serum albumin (BSA)). The pancreas was similarly incubated in MEM at 35°C. After 5 min incubation, a universal container was removed from the waterbath, shaken for 30 s, and the contents examined by incident white light microscopy. If a single cleaved (i.e. totally free of adherent exocrine tissue) islet was seen, the pancreas was removed from further incubation. If, however, no cleaved islets were present, further biopsies were examined at intervals of 2·5–7·5 min.

When cleaved islets were seen, the pancreas was removed from the incubation medium, placed into one-half of a kidney bowl divided by a 1-mm mesh, and gently teased apart with forceps. The digest that passed through the mesh was aspirated and passed through a 500-μm mesh into MEM at 4°C containing 20 per cent newborn calf serum (NBCS; Advanced Protein Products, Brierley Hill, UK) and 0·004 mg/ml DNAse. A further 50 ml MEM at 35°C containing 10 per cent NBCS was added to the kidney bowl, and the teasing and aspiration continued for 10–30 min until digestion ceased.

Automated digestion

The automated method utilized digestion of the collagenase-distended pancreas within an enclosed stainless steel digestion chamber (*Figure 1*). The half-pancreas was loaded into the chamber, together with seven steel ball-bearings of 1-cm diameter. The chamber was divided in two by a stainless steel mesh with 355-μm pores. By means of a polyvinyl chloride tubing circuit (COBE Laboratories, Gloucester, UK), MEM was recirculated at a rate of 50 ml/min through the chamber, with a heating circuit maintaining the temperature in the chamber at 35°C (recirculation phase). Once the medium started to recirculate, the chamber was agitated by a mechanical shaker to which it was attached, producing 300 vertical oscillations per min.

At 2–5-min intervals, 5-ml samples of the medium emerging from the chamber were taken from a side port of the tubing, stained with dithizone, and examined for the presence of cleaved islets. When

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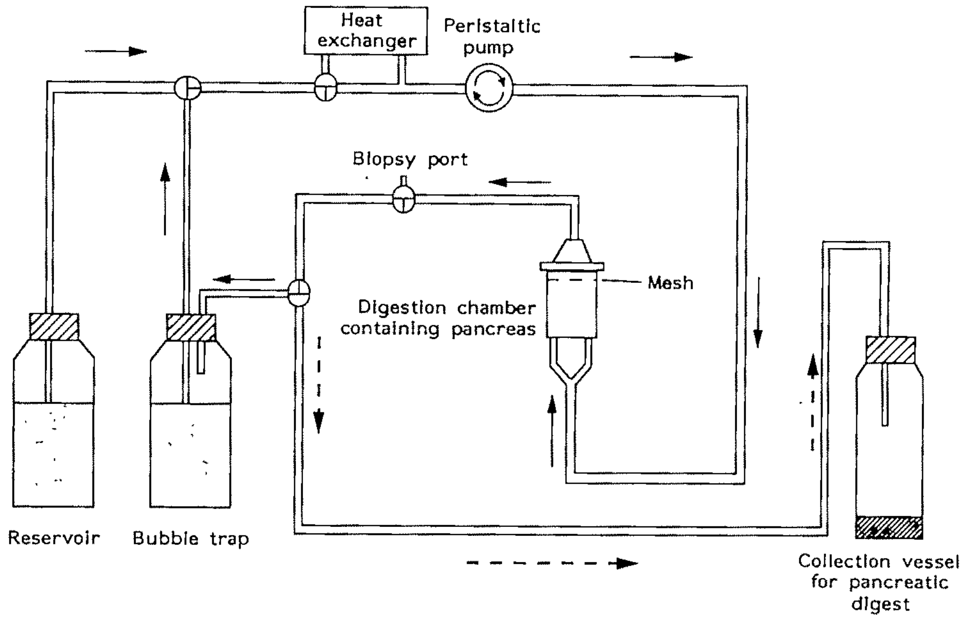
Heat exchanger
Peristaltic pump
Biopsy port
Mesh
Digestion chamber containing pancreas
Reservoir
Bubble trap
Collection vessel for pancreatic digest

Figure 1 *Circuitry used for the automated method of pancreas digestion. →, Direction of flow during recirculation phase; --→, diversion of flow during collection phase*

approximately ten islets were seen in a single microscopic field of × 100 magnification, the circuit was opened, enabling fresh medium (MEM–10 per cent DNAse) at 4°C to enter the chamber at a rate of 300 ml/min (collection phase). During this phase the chamber effluent was collected at 4°C into MEM containing 20 per cent NBCS. Digestion was judged complete when no further islets were seen in the biopsies from the chamber effluent.

Islet quantification

The non-distended weight of the two portions of the pancreas after longitudinal sectioning was calculated from the overall ratio of non-distended:distended weight multiplied by the weight of the distended portion of the gland. Islet yields are expressed per gram non-distended pancreas.

The digest produced by each method was washed three times in MEM–10 per cent NBCS, and suspended in a total volume of 50 ml. Five 200-μl samples were taken from the 50-ml tube, maintaining the tissue in suspension between samples by continuous shaking. Each of these samples was diluted tenfold with MEM in five separate universal containers and two 100-μl samples taken from these and separately placed on to a Petri dish, to give a total of ten samples from each digestion. Dithizone (100 μl) was added, the number of islets >50 μm in diameter counted in each sample, and the total number of islets calculated from the mean number per sample multiplied by the dilution factor. The mean volume of an islet was estimated by measuring 100 consecutive islet diameters using an eyepiece micrometer and calculating the volume of each islet ($0{\cdot}524 \times \text{diameter}^3$, assuming that islets are spherical). The total volume of islet tissue isolated was calculated as the product of the mean volume of an islet and their total number. Islet yield was corrected to '105-μm islet equivalents' by dividing the total islet tissue volume by the volume of an islet of 105 μm in diameter ($6{\cdot}1 \times 10^{-4}$ mm^3). This latter correction was made because studies from this laboratory on the size distribution of islets within pancreata from donor pigs have shown that 105 μm is the mean diameter of islets in histological section. This correction, therefore, equates to the 150-μm islet equivalent correction reported for human islet isolation studies. The percentage of cleaved (totally free of exocrine tissue) islets in the digest was estimated from inspection of the final samples.

Islet purification

After removal of the above samples, the final digests were centrifuged at 100*g* for 2 min and 100-μl aliquots suspended in 1 ml BSA (density 1·095 g/cm^3) in conical test tubes. These were overlain with a continuous linear density gradient of BSA, generated by a gradient maker (Hoefer Scientific Instruments, San Francisco, California, USA), containing in its chambers BSA of densities 1·069 and 1·095 g/cm^3, osmolality 400 mOsmol/kg. These gradients were then centrifuged at 500*g* for 20 min at 22°C and 11 × 1-ml aliquots aspirated carefully from the top to bottom of the gradients.

After washing these aliquots in MEM and resuspending the tissue in 2 ml MEM, each sample was sonicated for 20 s, 1 ml being stored for amylase assay while the other 1 ml underwent acid–alcohol extraction and subsequent storage for insulin assay. Amylase assay was by Phadebas Amylase Test Kit (Pharmacia Diagnostics, Uppsala, Sweden) and insulin was assayed by radioimmunoassay. The efficiency of density-gradient purification was assessed by plotting the cumulative percentage of amylase and insulin in these aliquots against density. The degree of exocrine (amylase) contamination at an islet (insulin) yield of 70 per cent was used as the criterion for comparison because this gave an estimate of islet purity when a reasonable yield of islets was obtained.

Islet viability studies

To confirm the viability of islets isolated by the automated method, purified islets from five consecutive automated isolations were transplanted to diabetic severe combined immunodeficient (Scid) mice, as previously described[11]. Briefly, the pancreatic digest was purified on large-scale BSA density gradients established on a COBE 2991 (COBE Laboratories, Lakewood, Colorado, USA) cell processor[3] and from each isolation two groups of 1000 islets were hand-picked and transplanted to the left renal subcapsular space of two diabetic (blood glucose >20 mmol/l) Scid mice. Mice were obtained from the National Institute of Medical Research (Mill Hill, London, UK) and rendered diabetic by intraperitoneal injection of streptozotocin (100 mg/kg on 3 consecutive days). Blood glucose was measured every 2 days after transplantation and the ability of the transplanted islets to reverse diabetes (blood glucose <10 mmol/l) confirmed by a return to the diabetic state after graft nephrectomy at 3 weeks.

Statistical analysis

Values are given as median (range); comparisons were performed using the Wilcoxon signed rank test for paired data.

Results

The results of the islet quantification experiments for the seven pancreata processed are summarized in *Table 1*. The absolute yield of islets per gram pancreas digested did not differ significantly between the two methods.

However, there were marked differences between the two procedures with respect to the other parameters of digestion studied. The islets produced by the automated method were significantly larger than those from the standard technique, as reflected in the higher mean volume of an islet, and so the former method produced a larger total volume of islet tissue per gram pancreas digested. This is most clearly expressed as the number of 105-μm islet equivalents per gram, which was

Table 1 *Islet quantification results for standard and automated methods of isolation*

	Standard method	Automated method	*T*	*P**
No. of islets per g pancreas	2698 (2013–5591)	4014 (2733–6920)	3·0	0·076
Mean volume of an islet ($\times 10^{-4}$ mm^3)	3·64 (2·12–6·34)	9·36 (4·39–11·20)	0·0	0·022
Total islet tissue volume (mm^3 per g pancreas)	1·07 (0·46–1·92)	3·56 (1·39–5·30)	0·0	0·022
105-μm islet equivalents per g pancreas	1766 (759–3168)	5875 (2294–8746)	0·0	0·022
Cleavage index (%)	82 (78–92)	92 (89–99)	1·0	0·035

Values are median (range). *Wilcoxon signed rank test for paired data

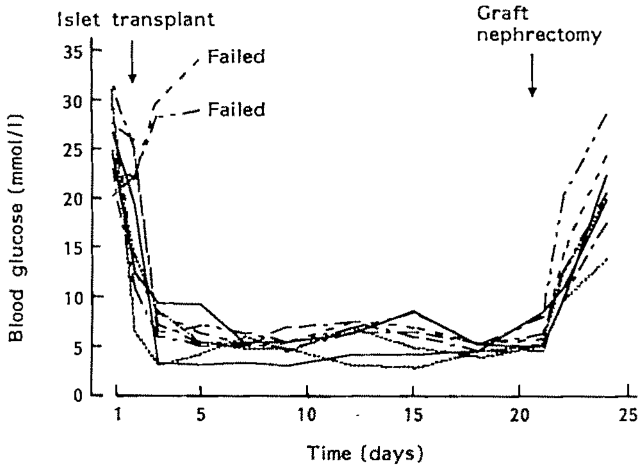

Figure 2 *Results of porcine islet transplantation to the diabetic Scid mouse. Islets (1000) from five consecutive isolations by the automated method were transplanted to the renal subcapsular space of two Scid mice. Isolation numbers: -----, 1; ——, 2; —— —, 3; – – –, 4; —--, 5. The ability of transplanted islets to reverse diabetes was confirmed by graft nephrectomy at 21 days*

significantly greater for the automated technique. Finally, the cleavage index was significantly higher with the automated method.

Results of the BSA density-gradient purification studies showed that the median (range) amylase contamination at a 70 per cent insulin yield for the automated method was 50 (4–95) per cent and for the manual method 34 (9–90) per cent ($P = 1·0$). *Figure 2* shows the outcome of the diabetic Scid mouse transplant studies performed to confirm the viability of islets isolated by the automated method. Diabetes was successfully reversed in eight of the ten mice. Although two grafts failed to reverse diabetes, they were from different islet preparations; the other paired transplant from the same preparation successfully reversed the diabetes in each case. This suggests that the problem was technical rather than the result of impaired islet viability.

Discussion

Porcine islets[5,12,13] are very fragile and the pig pancreas is therefore a good model in which to test the efficacy of methods purporting to produce effective digestion. The porcine pancreata used in the present study were obtained from abbatoir pork pigs under normal conditions of abbatoir operation. Although porcine islet isolation can be optimized by using a particular breed and age of pig and minimizing warm ischaemia time[14,15], the abbatoir pig remains a useful and readily available source of material with which to conduct studies applicable to human islet isolation.

A successful method of pancreatic collagenase digestion must disaggregate the gland while preserving the structure of the islets themselves. The intraductal route of collagenase delivery ensures that the enzyme is delivered directly into the pancreatic acini, thus acting first to dissociate exocrine from endocrine tissue. The key to production of large numbers of intact islets lies in exposure to collagenase for a critical time: long enough to allow their release from surrounding exocrine tissue but short enough to prevent digestion of the islets themselves. Because different pancreata vary widely with respect to their optimal collagenase digestion time, and because islets are susceptible to mechanical trauma, many existing methods of digestion are inadequate and produce marked islet fragmentation. This is particularly true in the case of porcine islet isolation.

The two methods compared in this study are recent adaptations of collagenase digestion, designed to attempt to overcome these problems. The manual biopsy-based method has the advantage of simplicity and requires little specialist equipment. It is the only non-automated technique based on individual 'tailoring' of the exposure of each pancreas to collagenase. The automated method has the advantage of continuous circulation of medium, allowing the progressive liberation of islets and their immediate protection from collagenase once liberated. It is, however, relatively complex to set up.

In this study a prospective comparison of these two widely used techniques was undertaken, dividing each pancreas and digesting the two halves by each method simultaneously. The size and distribution of islets is known to vary from the head to the tail of the gland[16] and the pancreata were therefore divided longitudinally to produce a similar islet population between the two methods. Thus, each pancreas acted as its own control, minimizing any adverse effects arising from the natural variation in collagenase digestion between different pancreata.

The absolute numbers of islets $>50\,\mu$m in diameter produced by the two techniques did not differ significantly and are comparable to those achieved by other groups using these methods[12–14]. Care must be taken when making such comparisons because porcine islets vary greatly with the age and strain of pig used[17], particularly with respect to size and fragility. It is not possible to measure islet fragmentation directly because small fragments are lost to waste during the washing stages of the isolation process. However, it can be concluded, because the mean volume of an islet, the total islet tissue volume and the number of 105-μm islet equivalents were significantly higher with the automated method, that most islets from the manual digestion were small and fragmented. In comparison, islets isolated by the automated method remained intact; their mean volume was comparable to the mean histological islet volume in the pancreas of donor pigs ($6·1 \times 10^{-4}$ mm^3).

The islet cleavage index was significantly higher with the automated method. This finding has important implications for subsequent islet purification because the density of uncleaved islets approaches that of adherent exocrine tissue, making it impossible to purify them by isopycnic density-gradient centrifugation. This result, taken in conjunction with the findings that the median amylase contamination at a 70 per cent insulin yield was no different between the manual and automated methods, and that there was a greatly increased volume of islet tissue in the digest from the automated procedure, means that the islet yield per gram original pancreas will be greater following purification with the automated than the manual method. Finally, the diabetic Scid mouse transplant studies show that the porcine islets produced by the automated method are viable and able to reverse diabetes. This finding is in agreement with the studies of Ricordi *et al.*[12], who showed that porcine islets produced by the automated method could reverse diabetes in nude mice.

In conclusion, this prospective study has shown that, compared with a standard manual method, the automated technique more than trebled the volume of islet tissue isolated from the porcine pancreas. Although the automated digestion method is relatively complex to set up, the greatly improved yield of intact islets justifies its routine use for porcine islet isolation.

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References

1. Gray DWR, Morris PJ. Developments in isolated pancreatic islet transplantation. *Transplantation* 1987; **43**: 321–31.
2. Gray DWR, McShane P, Grant A, Morris PJ. A method for isolation of islets of Langerhans from the human pancreas. *Diabetes* 1984; **33**: 1055–61.
3. London NJM, Lake SP, Wilson J *et al.* A simple but effective method for the controlled collagenase digestion of the human pancreas. *Transplantation* 1990; **49**: 1109–13.
4. Scharp D, Lacy P, Ricordi C *et al.* Human islet transplantation in patients with Type 1 diabetes. *Transplant Proc* 1989; **21**: 2744–45.
5. Ricordi C, Finke EH, Lacy PE. A method for the mass isolation of islets from the adult pig pancreas. *Diabetes* 1986; **35**: 649–53.
6. Alderson D, Kneteman NM, Scharp DW. The isolation of purified human islets of Langerhans. *Transplant Proc* 1987; **19**: 916–17.
7. Warnock GL, Cattral MS, Rajotte RV. Normoglycaemia after implantation of purified islet cells in dogs. *Can J Surg* 1988; **31**: 421–6.
8. Sutherland DER, Steffes MW, Bauer GE, McManus D, Noe BD, Najarian JS. Isolation of human and porcine islets of Langerhans and islet transplantation in pigs. *J Surg Res* 1974; **16**: 102–11.
9. Marchetti P, Zappella A, Giannarelli R *et al.* Isolation of islets of Langerhans from the adult pig pancreas. *Transplant Proc* 1988; **20**: 707–8.
10. Ricordi C, Lacy PE, Finke EH, Olack BJ, Scharp DW. Automated method for isolation of human pancreatic islets. *Diabetes* 1988; **37**: 413–20.
11. London NJM, Thirdborough ST, Swift SM, Bell PRF, James RFL. The diabetic 'human reconstituted' severe combined immunodeficient (SCID-hu) mouse: a model for isogeneic, allogeneic, and xenogeneic human islet transplantation. *Transplant Proc* 1991; **23**: 749.
12. Ricordi C, Socci C, Davalli AM *et al.* Application of the automated method to islet isolation in swine. *Transplant Proc* 1990; **22**: 784–5.
13. Ricordi C, Socci C, Davalli AM *et al.* Isolation of the elusive pig islet. *Surgery* 1990; **107**: 688–94.
14. Calafiore R, Calcinaro F, Basta G *et al.* A method for the massive separation of highly purified, adult porcine islets of Langerhans. *Metabolism* 1990; **39**: 175–81.
15. Ricordi C, Socci C, Davalli AM *et al.* Effect of pancreas retrieval procedure on islet isolation in the swine. *Transplant Proc* 1990; **22**: 442–3.
16. Marchetti P, Giannarelli R, Di Carlo A *et al.* Morphometrical and immunocytochemical characterisation of the porcine endocrine pancreas. *Transplant Proc* 1990; **22**: 727–8.
17. Socci C, Ricordi C, Davalli AM *et al.* Selection of donors significantly improves pig islet isolation. *Horm Metab Res* 1989; **25**(Suppl): 32–4.

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Selective cholangiography in laparoscopic cholecystectomy

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Laparoscopic cholecystectomy is now the method of choice for removing the diseased gallbladder. Asymptomatic common bile duct stones occur in approximately 6 per cent of patients. Controversy exists, however, as to whether selective or routine peroperative cholangiography should be performed during laparoscopic cholecystectomy. Over a 21-month period 300 consecutive laparoscopic cholecystectomies without routine cholangiography were attempted. There were 28 conversions. In all, 229 patients did not undergo cholangiography and in this group there were two common duct injuries. These were both identified and dealt with by open operation. Five patients underwent peroperative cholangiography, none of whom was found to have common duct pathology. Endoscopic retrograde cholangiopancreatography was performed in 38 patients. Of 27 who had this investigation performed before operation, common duct stones were diagnosed in seven (26 per cent). Two common duct stones were discovered in 11 patients who underwent the investigation after operation. Thus only two of 240 patients (0·8 per cent) who did not undergo preoperative or peroperative cholangiography subsequently had symptomatic duct stones. Peroperative cholangiography may be indicated in selected patients who have had symptoms of common bile duct stones or in those in whom the biliary anatomy is unclear. However, routine preoperative or peroperative cholangiography is unnecessary during laparoscopic cholecystectomy.

Laparoscopic cholecystectomy is a minimally invasive technique for removal of the diseased gallbladder, with several theoretical advantages over traditional open cholecystectomy[1,2]. However, the advent of this technique has refocused attention on the management of common bile duct (CBD) stones[3]. Symptomatic choledocholithiasis may now be managed by preoperative endoscopic retrograde cholangiopancreatography (ERCP) followed by laparoscopic cholecystectomy or by peroperative exploration of the CBD during traditional or laparoscopic cholecystectomy. The incidence of unsuspected duct stones varies from 1·2 to 14 per cent[4] and, while controversy has always existed as to whether routine or selective cholangiography should be performed[5], most British surgeons have recently performed routine cholangiography during open cholecystectomy[6]. However, little is known about the natural history of unsuspected CBD stones and controversy exists as to whether routine cholangiography prevents bile duct injury. A policy of selective cholangiography during laparoscopic cholecystectomy has been adopted in this department and in this study the outcome of this policy in 300 consecutive procedures is analysed.

Patients and methods

Between February 1990 and October 1991, 300 patients underwent elective laparoscopic cholecystectomy at this hospital. There were 65 men and 235 women with a mean(s.d.) age of 47·7(14·5) (range 17–78) years and a mean(s.d.) weight of 71·3(13·7) kg. Mean age and weight did not vary beween the first, second and third hundred patients. Indications for laparoscopic cholecystectomy are shown in *Table 1*. No patient underwent the operation for asymptomatic gallstones. Cholelithiasis was confirmed in all patients by ultrasonography before operation. Details of the operative technique of laparoscopic cholecystectomy have previously been described[1]. Briefly, a four-cannula technique (occasionally three) was used; the cystic duct was identified, doubly clipped and divided, and a similar approach then used to clip and divide the cystic artery. The gallbladder was separated from the gallbladder bed using diathermy and removed through one of the 10-mm cannulas. The subhepatic space was irrigated with 500 ml saline and no drains were placed.

A policy of selective cholangiography was followed for patients undergoing laparoscopic cholecystectomy. The indications for cholangiography before or during operation were: (1) a history of jaundice; (2) a history of cholangitis including jaundice, fever and rigors; (3) any abnormal liver function test result; (4) a CBD diameter >10 mm determined by ultrasonography; (5) CBD calculi on ultrasonography; and (6) gallstone pancreatitis. The indications for cholangiography in the postoperative period were a history of jaundice or abnormal liver function test results since the time of surgery. The

Table 1 *Indications for laparoscopic cholecystectomy in 300 consecutive patients*

Indication	Patient nos 1–100	101–200	201–300	Total
Gallstone pancreatitis	8	4	9	21 (7·0)
Acute cholecystitis	23	18	16	57 (19·0)
Chronic cholecystitis	27	26	30	83 (27·7)
Biliary colic	42	52	45	139 (46·3)

Values in parentheses are percentages

Table 2 *Reasons for conversion to open cholecystectomy*

Indication for operation	Unsafe anatomy	Bleeding	Other	Total
Gallstone pancreatitis	0	0	0	0
Acute cholecystitis	12	1	2	15
Chronic cholecystitis	5	3	0	8
Biliary colic	2	1	2	5
Total	19	5	4	28

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Table 3 *Results of selective cholangiography in 272 patients who underwent laparoscopic cholecystectomy*

	Cholangiography		ERCP		
	None	Peroperative	Preoperative	Postoperative	Total
No. of patients	229	5	27	11	272
No. with positive investigation	0	0	7 (26)	2 (18)	9 (3·3)
No. with duct injury	2	0	0	0	2 (0·7)

Values in parentheses are percentages. ERCP, endoscopic retrograde cholangiopancreatography

choice between preoperative ERCP or peroperative cholangiography was left to the consultant looking after the patient. All patients were followed up after operation for a period ranging from 7 to 26 (mean 12) months.

Results

Of the 300 patients undergoing laparoscopic cholecystectomy, 28 operations were converted to an open procedure. Nineteen operations were converted because of unclear anatomy where further dissection was deemed hazardous. In five patients a minilaparotomy was performed to control bleeding. Instrument failure resulted in conversion to open operation in three patients early in the series and one patient had open cholecystectomy because carcinoma of the gallbladder was suspected (*Table 2*). In total, 272 patients underwent successful laparoscopic cholecystectomy.

In all, 229 patients did not have cholangiography (*Table 3*). In this group there were two common duct injuries, both of which occurred early in the dissection, before the point at which operative cholangiography would have been performed. In the first case the injury occurred in the hands of a junior operator in a patient with chronic cholecystitis, while the second happened as an experienced senior operator was attempting to dissect the cystic duct in an acutely inflamed gallbladder. In neither case was the duct transected and in both patients the latter was easily repaired by simple suture and placement of a T tube. Subsequent cholangiography in both patients showed a normal biliary tree. However, at 10 months one patient had a narrowed segment in the CBD at the level of the injury, although the results of liver function tests were normal.

Peroperative laparoscopic cholangiography was performed in five patients, in none of whom was any common duct pathology revealed. Preoperative visualization of the biliary tree using ERCP was performed successfully in 27 patients, of whom seven (26 per cent) had CBD stones. All seven patients were successfully treated by sphincterotomy during ERCP. Postoperative ERCP was performed in 11 patients and was positive in two. In the other nine patients a normal CBD was demonstrated. In total there were nine symptomatic common duct stones and two CBD injuries. Of 240 patients who did not undergo preoperative or peroperative cholangiography, as yet only two (0·8 per cent) have returned with symptomatic CBD stones.

Discussion

Laparoscopic cholecystectomy is now the treatment of choice for symptomatic gallstone disease in most major centres[1,2,7–9]. In the present study, 240 of 272 patients (88·2 per cent) submitted to laparoscopic cholecystectomy did not undergo either preoperative or peroperative cholangiography. Subsequently 11 patients returned with symptoms sufficient to warrant postoperative ERCP. However, only three patients developed jaundice after operation and of these only two had CBD stones at ERCP. Both patients were successfully treated by endoscopic sphincterotomy (ES). Jaundice in the third resolved spontaneously and findings at ERCP in this patient were normal. Thus, at a mean follow-up of 12 months, only two of the 240 patients (0·8 per cent) have returned with symptomatic retained CBD stones.

The incidence of common duct stones is about 12 per cent in patients undergoing cholecystectomy[10]. Unsuspected CBD stones occur in 1·2–14 per cent of patients, with a mean of 6 per cent[4]. However, Yip and colleagues have suggested that the incidence of unsuspected stones has been overestimated and, in an analysis of 356 patients undergoing cholecystectomy with routine cholangiography, they detected no unsuspected common duct calculi[11]. The natural history of unsuspected CBD stones is unknown, but a number of reports have documented the spontaneous passage of stones into the duodenum[12–16]. Older reports of cholecystectomy without cholangiography suggest that only 0·3 per cent of patients will subsequently return with biliary problems[17–19]. More recently, Voyles and colleagues reported that only two of 249 patients (0·8 per cent) had a clinical episode following laparoscopic cholecystectomy suggesting a retained stone[20]. The results of the present analysis are consistent with these observations. Only 0·8 per cent of patients who did not undergo cholangiography returned with symptomatic CBD stones at a mean of 12 months after laparoscopic cholecystectomy. Such stones can be managed safely and efficiently by ES[21]. We suggest that, analogous to the current approach to asymptomatic gallbladder calculi[22], silent CBD stones should not be treated until they become symptomatic.

Significant anatomical variation of the biliary tree may predispose to iatrogenic duct injury if it is not identified before dissection of Calot's triangle. Variation in biliary anatomy has been recorded in 3–15 per cent of individuals[23]. Advocates of routine peroperative cholangiography maintain that demonstration of biliary anatomy reduces the chance of iatrogenic duct injury. Data from retrospective series have shown that approximately 0·3–0·5 per cent of patients undergoing open cholecystectomy sustain bile duct injury[24–26], although advocates of routine cholangiography have reported rates as low as 0·1 per cent[27]. Similar incidences of duct injury have been reported in series of laparoscopic cholecystectomy in which routine (0·3–0·6 per cent)[28,29] or selective (0 per cent)[20] cholangiography was used. In their experience with selective cholangiography the present authors have had two duct injuries in over 400 laparoscopic cholecystectomies (0·5 per cent). Both occurred early in the dissection around the cystic duct, before the point at which cholangiography would have been performed. Subsequent cholangiography showed that there was no anatomical abnormality in the biliary system in either patient. In neither case was the duct transected and repair was easily achieved in both patients. Thus, we believe that the use of routine cholangiography would not have prevented these injuries. The risk of CBD injury can be minimized by assiduous attention to detail in the dissection of the cystic duct–gallbladder junction. We agree completely with Ponsky[30] that 'the cystic duct should be unequivocally traced up onto the gallbladder prior to any clipping or division'. If the anatomy is still unclear then cholangiography is indicated and the surgeon should have a low threshold for conversion to open surgery in this situation.

Operative cholangiography is not an ideal investigation: up to 50 per cent of cholangiograms are associated with technical errors[31], while up to 30 per cent of films are unsatisfactory for decision making[32], leading to a mean false-positive cholangiography rate of 3 per cent[33]. False-positive cholangiograms, in addition to leading to unnecessary bile duct exploration or ERCP, are associated with higher morbidity, mortality and cost[4,11,12,19–34,35]. Using a policy of selective cholangiography, up to two-thirds of CBD explorations can be avoided[11]. Furthermore, operative cholangiography does not eliminate the problem of retained stones after common duct exploration and values of up to 22 per cent have been reported[36].

Operative cholangiography is expensive, although accurate calculation of costs is difficult. In 1986, Gerber[4] estimated the cost of peroperative cholangiography at US $500 (£300) and calculated that the detection of one unsuspected but clinically important CBD stone cost US $166 500 (£100 000). Although Voyles *et al.*[20] have calculated that laparoscopic cholangiography is slightly less expensive at US $300 (£180), we must agree with Gerber's conclusion that 'at best routine operative cholangiography obviously is not cost effective and at worst, is an unconscionable waste of money'[4]. Moreover, Holmin and colleagues showed that selective operative cholangiography would lead to a saving of 4·5 per cent of the expected hospital costs[35].

We advocate that cholangiography be performed only in selected patients who have either clinical or biochemical evidence of CBD stones or in whom there is a real concern about the anatomy of the biliary tree. A recent review of this controversial area reached similar conclusions[37]. If there are any doubts about the relationship of the structures in Calot's triangle, traditional open cholecystectomy should be performed. Until more is known about the natural history of CBD stones it seems inappropriate to perform an investigation that may be required in only a small proportion of patients undergoing laparoscopic cholecystectomy.

References

1. Grace PA, Qureshi A, Coleman J *et al.* Reduced postoperative hospitalization after laparoscopic cholecystectomy. *Br J Surg* 1991; **78**: 160–2.
2. Nathanson LK, Shimi S, Cuschieri A. Laparoscopic cholecystectomy: the Dundee technique. *Br J Surg* 1991; **78**: 155–9.
3. McEntee G, Grace PA, Bouchier-Hayes D. Laparoscopic cholecystectomy and the common bile duct. *Br J Surg* 1991; **78**: 385–6.
4. Gerber A. A requiem for the routine operative cholangiogram. *Surg Obstet Gynecol* 1986; **163**: 363–4.
5. Scott-Coombes D, Thompson J. Bile duct stones and laparoscopic cholecystectomy. *BMJ* 1991; **303**: 1281–2.
6. Cahill CJ, Pain JA. Current practice in biliary surgery. *Br J Surg* 1988; **75**: 1169–72.
7. Dubois F, Icard P, Berthelot G, Levard H. Celioscopic cholecystectomy. Preliminary report of 36 cases. *Ann Surg* 1991; **211**: 60–3.
8. The Southern Surgeons Club. A prospective analysis of 1518 laparoscopic cholecystectomies. *N Engl J Med* 1991; **324**: 1073–8.
9. Paterson-Brown S, Garden OJ, Carter DC. Laparoscopic cholecystectomy. *Br J Surg* 1991; **78**: 131–2.
10. Britton BJ. The management of stones in the common bile duct. In: Taylor I, ed. *Progress in Surgery*. Vol. 2. Edinburgh: Churchill Livingstone, 1987: 86–98.
11. Yip AWC, Ng WS, Chow WC, Choi TK, Lam KH. Plea for selective operative cholangiography. *J R Coll Surg Edinb* 1991; **36**: 21–4.
12. Stark ME, Loughry CW. Routine operative cholangiography with cholecystectomy. *Surg Gynecol Obstet* 1980; **151**: 657–8.
13. Longmire WP. The diverse causes of biliary obstruction and their remedies. *Curr Probl Surg* 1977; **14**: 12–19.
14. Johnson CD, Celestin LR. Large gallstones may pass spontaneously. *J R Soc Med* 1985; **78**: 305–7.
15. Heiken TJ, Birkett DH. Postoperative T-tube tract choledochoscopy. *Am J Surg* 1992; **163**: 28–31.
16. Soravia C, Meyer P, Mentha G, Ambrosetti P, Rohner A. Flushing technique in the management of retained common bile duct stones with a T tube *in situ*. *Br J Surg* 1992; **79**: 149–51.
17. Bartlett MK, Quimby WC. Mortality and complications of cholecystectomy and choledochotomy for chronic cholecystitis. *N Engl J Med* 1956; **254**: 154–6.
18. Glenn F, McSherry CK. Calculus biliary tract disease. *Curr Probl Surg* 1975; **12**: 26–33.
19. Gerber A, Apt MK. The case against routine operative cholangiography. *Am J Surg* 1982; **143**: 734–6.
20. Voyles CR, Petro AB, Meena AL, Haick A, Koury AM. A practical approach to laparoscopic cholecystectomy. *Am J Surg* 1991; **161**: 365–70.
21. Cotton PB. Progress report. ERCP. *Gut* 1977; **18**: 316–41.
22. Gibney EJ. Asymptomatic gallstones. *Br J Surg* 1990; **77**: 368–72.
23. Goor DA, Ebert PA. Anomalies of the biliary tree. *Arch Surg* 1972; **304**: 102–9.
24. Herman RE. A plea for a safer technique of cholecystectomy. *Surgery* 1976; **79**: 609–11.
25. Smith EB. Iatrogenic injuries to extrahepatic bile ducts and associated vessels: a 25 year analysis. *J Natl Med Assoc* 1982; **74**: 735–8.
26. Andren-Sandberg A, Alinder G, Bengmark S. Accidental lesions of common bile duct at cholecystectomy. *Ann Surg* 1985; **201**: 328–32.
27. Berci G, Sackier JM, Paz-Partlow M. Routine or selective intraoperative cholangiography during laparoscopic cholecystectomy. *Am J Surg* 1991; **161**: 355–60.
28. Bailey RW, Zucker KA, Flowers JL, Scovill WA, Graham SM, Imbembo AL. Laparoscopic cholecystectomy. Experience with 375 consecutive patients. *Ann Surg* 1991; **214**: 531–41.
29. Berci G, Sackier J, Phillips E, Shapiro S, Paz-Partlow M. Laparoscopic cholecystectomy. Anomalies and bile duct injuries. *World Congress of Surgery, Stockholm* 1991: 142.
30. Ponsky JL. Complications of laparoscopic cholecystectomy. *Am J Surg* 1991; **161**: 393–5.
31. Rolfsmyer ES, Bubrick MP, Kollitz PR *et al.* The value of operative cholangiography. *Surg Gynecol Obstet* 1982; **154**: 369–71.
32. Macintyre IMC, Goulborne IA, Gollock JM, Greive DC. Operative cholangiography: a study of observer variation. *J R Coll Surg Edinb* 1988; **33**: 65–7.
33. Mills JL, Beck DE, Harford EJ. Routine operative cholangiography. *Surg Gynecol Obstet* 1985; **161**: 343–5.
34. White TT, Hart MJ. Cholangiography and small duct injury. *Am J Surg* 1985; **149**: 640–3.
35. Holmin T, Jonsson B, Lingren B *et al.* Selective or routine operative cholangiography: a cost effectiveness analysis. *World J Surg* 1980; **4**: 315–22.
36. Corlette MB Jr, Schatzki S, Ackroyd F. Operative cholangiography and the overlooked stones. *Arch Surg* 1978; **113**: 729–34.
37. Corder AP, Scott SD, Johnson CD. Place of routine operative cholangiography at cholecystectomy. *Br J Surg* 1992; **79**: 945–7.

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Short note

Br. J. Surg. 1993, Vol. 80, February, 247

Laparoscopic cholecystectomy with endoscopic retrograde cholangiopancreatography for acute gallstone pancreatitis

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Cholecystectomy is advocated after gallstone pancreatitis to prevent recurrent attacks. Surgery is recommended during the same admission because many patients develop recurrent pancreatitis while waiting for cholecystectomy[1,2]. The management of common bile duct (CBD) calculi in patients with acute pancreatitis has been revolutionized by the finding that endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) during the early stages of an attack of pancreatitis are not only safe but improve outcome in patients with severe disease[3].

Laparoscopic cholecystectomy has rapidly become established as the treatment of choice for cholelithiasis in many hospitals in the UK. Because laparoscopic exploration of the CBD is still in its infancy, ERCP and ES are generally used to detect and treat choledocholithiasis in patients having gallbladder stones treated by laparoscopic cholecystectomy[4]. A logical approach to acute gallstone pancreatitis would be to combine early ERCP and ES followed by laparoscopic cholecystectomy when the CBD is clear of stones. This method has been studied prospectively in 16 consecutive patients with acute gallstone pancreatitis.

Patients and methods

Sixteen consecutive patients (six men, ten women) of median age 55·5 (range 25–80) years were studied. A diagnosis of acute gallstone pancreatitis was based on history, clinical examination, serum amylase level >1000 units/ml, and demonstration of gallstones by ultrasonography within 24 h of admission. The severity of disease was assessed according to the criteria of Blamey *et al.*[5]. In cases of severe pancreatitis, ERCP was undertaken on the next available list, whereas in mild disease it was performed a few days later after the attack had settled. When the common duct had been cleared, laparoscopic cholecystectomy was performed on the next available routine operating list.

Results (*Figure 1*)

Of the 16 patients, 12 had mild pancreatitis and four severe disease; six were jaundiced at admission. ERCP was undertaken a median of 4 (range 1–9) days after admission. Cannulation of the CBD was achieved in 12 patients during the first ERCP procedure and in three at the second attempt (one required intravenous cholangiography to confirm that the CBD was clear). Stones were found in seven patients, two with severe disease. Calculi were cleared after ES in four patients during the first ERCP procedure and in three duct clearance was confirmed at repeat ERCP 8, 11 and 18 days after admission. ERCP took a median of 30 (range 20–45) min and there were no complications attributed to it.

Laparoscopic cholecystectomy was performed a median of 10 (range 4–34) days after admission. Four patients were allowed home after ERCP and ES and readmitted as soon as possible for operation. The median operating time for cholecystectomy was 50 (range 30–120) min; gallstones were found in all patients. Two patients had fluid collections visible at laparoscopy; these settled over a 10-week period. There were no complications attributable to laparoscopic cholecystectomy. The median postoperative stay was 2 (range 1–3) days and return to work or normal activities was achieved within a median of 10 (range 5–20) days. The mean total hospital stay was 9·5 (range 5–22) days.

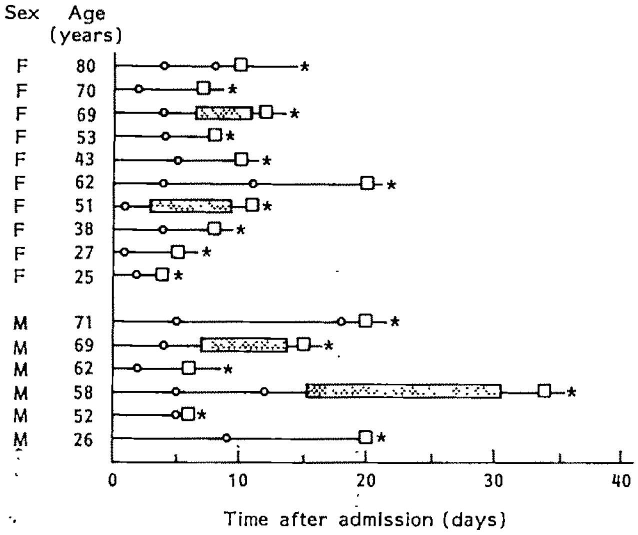

Figure 1 *Details of 16 patients with gallstone pancreatitis.* ○, *Endoscopic retrograde cholangiopancreatography (ERCP);* □, *laparoscopic cholecystectomy;* *, *discharge from hospital;* ▨, *patient allowed home between ERCP and laparoscopic cholecystectomy*

Discussion

If cholecystectomy is delayed by 3 months after gallstone pancreatitis, up to 50 per cent of patients will suffer recurrent attacks of pancreatitis. However, cholecystectomy within 48 h of admission is associated with an increased mortality rate[6]. Since ERCP is safe and may improve outcome in severe pancreatitis, this is advocated early in patients admitted with gallstone pancreatitis. When the CBD is cleared of stones, laparoscopic cholecystectomy may be performed safely. This minimally invasive approach to gallstone pancreatitis provides definitive treatment during a single hospital admission, reduces the likelihood of recurrent pancreatitis and allows a shorter recovery period before return to work.

References

1. Kelly TR. Gallstone pancreatitis: the timing of surgery. *Surgery* 1980; **88**: 345–50.
2. Osborne DH, Imrie CW, Carter DC. Biliary surgery in the same admission for gallstone-associated acute pancreatitis. *Br J Surg* 1981; **68**: 758–61.
3. Neoptolemos JP, Carr-Locke DL, London NJ, Bailey IA, James D, Fossard DP. Results of a controlled trial of urgent ERCP and endoscopic sphincterotomy in patients with pancreatitis due to gallstones. *Lancet* 1988; **ii**: 979–83.
4. Scott-Coombes D, Thompson JN. Bile duct stones and laparoscopic cholecystectomy. *BMJ* 1991; **303**: 1281–2.
5. Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. *Gut* 1984; **25**: 1340–6.
6. Kelly TR, Wagner DS. Gallstone pancreatitis: a prospective randomized trial of the timing of surgery. *Surgery* 1988; **104**: 600–5.

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Transanal division of an apical pouch bridge after restorative proctocolectomy with a J shaped reservoir

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Restorative proctocolectomy with construction of an ileal reservoir has been used in the past two decades for the treatment of ulcerative colitis and familial adenomatous polyposis (FAP). The J shaped ileal reservoir developed by Utsunomiya *et al.*[1] is widely used[2]. The J pouch has an adequate size, with a capacity similar to that of the normal rectum (300–400 ml), and empties well without the need for catheterization[3,4].

Excellent functional outcome is achieved in patients with ulcerative colitis and FAP following restorative proctocolectomy with construction of a J pouch[3,4]. However, functional imperfections are still frequent; the causes of such impairment are sphincter damage, insufficient reservoir capacity and improper pouch dynamic characteristics. Recently, Schoetz *et al.*[5] and Öresland and colleagues[6] have reported an apical pouch bridge syndrome in which three and six patients, respectively, experienced tenesmus and bleeding on evacuation after restorative proctocolectomy with construction of a J shaped reservoir. Öresland *et al.*[6] described the unsplit apical pouch bridge of the J shaped reservoir emerging through the anus during straining. This bridge caused outlet obstruction. This paper describes a technique for division of such an apical pouch bridge.

Surgical technique

The J pouch was constructed from two ileal limbs (each 20-cm long) using the GIA (Auto Suture, Norwalk, Connecticut, USA) stapling apparatus. Two small transverse enterotomies were made halfway along both ileal limbs. Through these enterotomies, the stapler was fired sequentially towards the apex and base of the pouch. The resulting septum was left *in situ*.

Transanal apical pouch bridge division was performed under lumbar anaesthesia. The patient was placed in the prone jack-knife position and the anus gently dilated with anal retractors to expose the ileoanal anastomosis. Two Nelaton catheters (vinyl chloride drains; Terumo, Tokyo, Japan) were used to anchor the apical pouch bridge after it had been pulled out of the anus. The apical bridge was then divided using a GIA50 stapler (*Figure 1*).

Results

Between August 1984 and December 1991, 109 restorative proctocolectomies with construction of a J shaped reservoir have been performed, in 65 patients with ulcerative colitis and 44 with FAP; five patients (5 per cent) with the apical pouch bridge syndrome have been encountered.

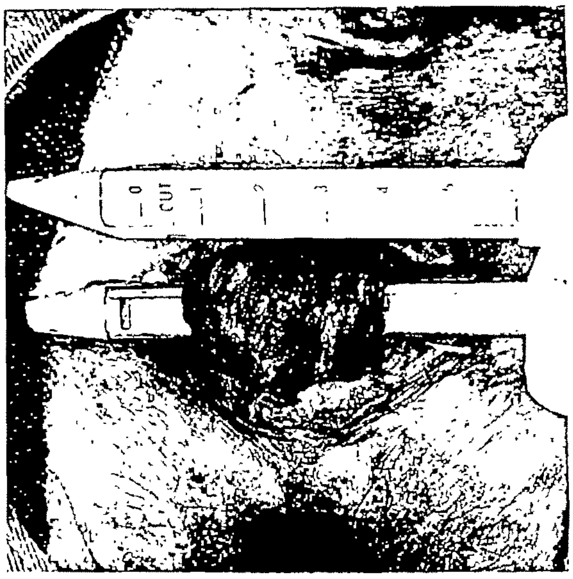

Figure 1 *Insertion of the GIA50 stapler below the apical pouch bridge before division*

After an uncomplicated postoperative course, all five patients presented 2–5 years later with evacuation difficulties in the sitting position, while straining at stool. Peranal bleeding was usually noted. Digital examination revealed no anastomotic stricture and there was no endoscopic evidence of inflammatory changes in the mucosa. Pouchography revealed slight dilatation of the ileal reservoir and evacuation pouchography showed that the unsplit apical pouch bridge prolapsed to cover the anal canal when the patient strained in the sitting position.

Discussion

The apical pouch bridge acted to block the reservoir outflow and sometimes prolapsed through the anus[6]. On review at 6 months after division of the bridge, symptoms related to defaecation had resolved completely.

It is very simple to divide the apical pouch bridge as described. The patient's symptoms are dramatically improved by this procedure, with a good functional result. This pitfall should be taken into account by surgeons when deciding on the construction of a J pouch.

References

1. Utsunomiya J, Iwama T, Imajo M *et al.* Total colectomy, mucosal proctectomy, and ileoanal anastomosis. *Dis Colon Rectum* 1980; **23**: 459–66.
2. Dozois RR, Goldberg SM, Rothenberger DA *et al.* Restorative proctocolectomy with ileal reservoir. *Int J Colorectal Dis* 1986; **1**: 2–19 (Symposium).
3. Utsunomiya J, Yamamura T, Kusunoki M, Iwami T. The current technique for ileoanal anastomosis. *Digestive Surgery* 1988; **5**: 207–14.
4. Pemberton JH, Kelly KA, Beart RW, Dozois RR, Wolff BG, Ilstrup DM. Ileal pouch–anal anastomosis for chronic ulcerative colitis. *Ann Surg* 1987; **206**: 504–13.
5. Schoetz DJ Jr, Coller JA, Veideenheimer MC. Can the pouch be saved? *Dis Colon Rectum* 1988; **31**: 671–5.
6. Öresland T, Fasth S, Nordgren S, Hultén L. The clinical and functional outcome after restorative proctocolectomy. *Int J Colorectal Dis* 1989; **4**: 50–6.

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Individuals with a strong family history of colorectal cancer demonstrate abnormal rectal mucosal proliferation

Thirty-seven individuals with an increased lifetime risk of colorectal cancer because of family history and a control group ($n = 21$) *with no such family history underwent colonoscopy. No neoplastic lesion was found in any individual. Rectal biopsies of macroscopically normal mucosa were taken 8 cm from the anal margin and mucosal proliferation assessed by the crypt cell production rate (CCPR). There was no difference in CCPR between the control group (median 10 (95 per cent confidence interval 7–11) cells per crypt per h) and those at intermediate risk (lifetime risk between 1:17 and 1:10,* $n = 14$*). However, there was a significant difference in CCPR between the control group and those at higher risk (lifetime risk >1:10,* $n = 23$*) (median CCPR 13 (95 per cent confidence interval 10–17) cells per crypt per h,* $P = 0{\cdot}004$*). A high risk of colorectal cancer derived from family history correlates with an increased colorectal mucosal proliferation rate.*

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There is evidence linking colorectal mucosal proliferation and large bowel neoplasia[1–6]. Individuals belonging to kindreds with an autosomal dominant inheritance of familial adenomatous polyposis (FAP) or hereditary non-polyposis colorectal cancer have been identified, and rectal mucosal proliferation in these individuals is increased compared with that in controls without such a family history[5,6]. Hyperproliferation may, therefore, be the first step in the transformation from flat normal mucosa to neoplastic tissue. Fearon and Vogelstein, from genetic work in FAP, postulated deletions of 5q leading to hyperproliferation of colorectal mucosa in individuals free of neoplasia[7].

The genetic link was first studied by Warthin, who described a familial aggregation of patients with colorectal cancer[8]. Detailed study of pedigrees allows individuals at risk of such cancer to be identified, and a mathematical lifetime risk of disease can be calculated based on the age and number of relatives affected within the kindred. The risk ranges[9,10] from an autosomal dominantly inherited risk of 1:2, to 1:10 where there is one affected relative under the age of 45 years, to a lower intermediate risk of 1:17 where one relative affected is over the age of 45 years, to a population risk of 1:50.

This study correlates individual calculated cancer risks with biomarker proliferation indices for a heterogeneous group of individuals presenting to a family history of colorectal cancer screening clinic. Rectal mucosal proliferation was measured using the metaphase arrest technique because of its simplicity and technical advantages over the labour-intensive tritiated thymidine procedure. The method used was based on those previously described[11–15].

Patients and methods

Thirty-seven individuals with a family history of colorectal cancer were identified and the personal risk of such cancer calculated from a detailed family history. They were stratified into high- (>1:10 lifetime risk) and intermediate- (lifetime risk between 1:10 and 1:17) risk groups (*Figure 1*). All subjects in the family history group were shown to be free of neoplasia by total colonoscopy. Twenty-three individuals were in the high-risk group and 14 in the intermediate group. Twenty-one individuals without tumours on colonoscopy but with no family history were identified to act as a control group with a population risk of colorectal cancer (1:50).

Control subjects underwent colonoscopy because they had had a positive faecal occult blood test, an equivocal barium enema finding or hyperplastic polyps.

Endoscopic biopsies were taken 8 cm from the anal margin. The bowel preparation in these subjects was Klean-prep (Norgine, Oxford, UK), which has minimal effect on mucosal proliferation and histology, unlike senna preparations[16,17]. Normal rectal mucosa was confirmed by histological examination in all cases.

Mucosal proliferation was measured by the metaphase arrest technique and the crypt cell production rate (CCPR) calculated[11–14]. Biopsies were divided into 2-mm portions (explants) and placed in tissue culture medium RPMI 1640 (Gibco, Paisley, UK) to which was added 0·001 per cent gentamicin and 10 per cent fetal calf serum (Sigma Chemicals, Poole, UK). Samples were stored overnight (18 h) to allow for any extraction artefact[12,13]. At the time of assay the organ culture medium was replaced with fresh medium containing 1 ml 5 μg/ml vincristine. The culture medium containing the explants was incubated in an atmosphere of 5 per cent carbon dioxide–95 per cent oxygen.

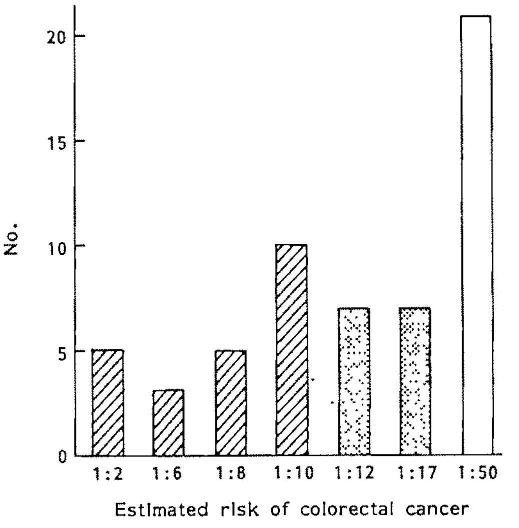

Figure 1 *Number of individuals and calculated colorectal cancer risks.* □, *Controls* ($n = 21$); ■, *high-risk individuals* ($n = 23$); ░, *Intermediate-risk individuals* ($n = 14$)

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Explants were removed from tissue culture at 25-, 50- and 75-min timepoints, fixed in Carnoy's solution for 2–4 h and then stored in 70 per cent ethanol. The tissue was rehydrated and stained as described by Barsoum *et al.*[18]. The number of metaphase arrests was counted in 20–30 crypts. The CCPR was calculated from least squares regression analysis of the data points and expressed as cells per crypt per hour.

Approval was granted by the ethical committee of University Hospital, Nottingham, and informed consent obtained from all individuals in the study.

Statistical analysis

Proliferation data were compared using the Mann–Whitney *U* test. A 95 per cent confidence interval (c.i.) was calculated. Comparisons of age employed Student's unpaired *t* test.

Results

The study populations and estimated cancer risks are shown in *Figure 1*. The median (95 per cent c.i.) age of the study group was 41 (19–68) years, significantly less than that of the control group of 57 (39–71) years ($t = 4{\cdot}9$, 56 d.f., $P = 0{\cdot}00001$).

There was no difference in CCPR between the intermediate-risk group and controls (*Figure 2*). The high-risk group had a significantly higher median (95 per cent c.i.) CCPR than the control group (13 (10–17) *versus* 10 (7–11) cells per crypt per h, $P = 0{\cdot}004$) (*Figure 3*). Using the 95th centile of the control group data (CCPR 15 cells per crypt per h), a cut-off may be applied to define the upper limit of normal proliferation. Applying this cut-off to the high-risk group, ten individuals lying outside the normal range can be identified, i.e. with hyperproliferation (*Figure 3*).

From *Figure 1* the number of individuals who might expect to develop colorectal cancer in the high-risk group (expected cancer phenotype) can be calculated. For this particular group, two from the 1:2 group and two from the other 18 patients in the high-risk group are identified, giving an expected cancer phenotype for approximately four individuals.

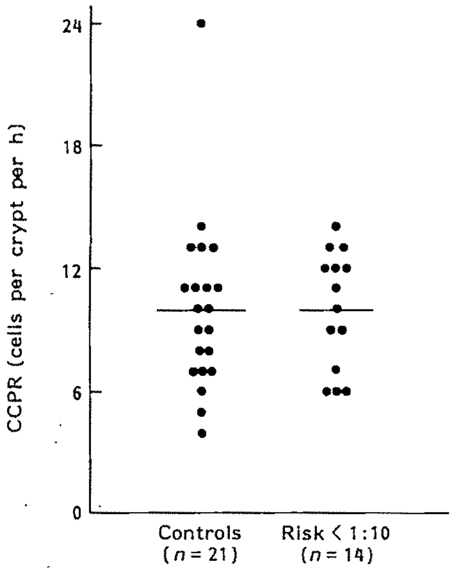

Figure 2 *Relationship between crypt cell production rate (CCPR) and intermediate lifetime risk of colorectal cancer. Bars are medians*

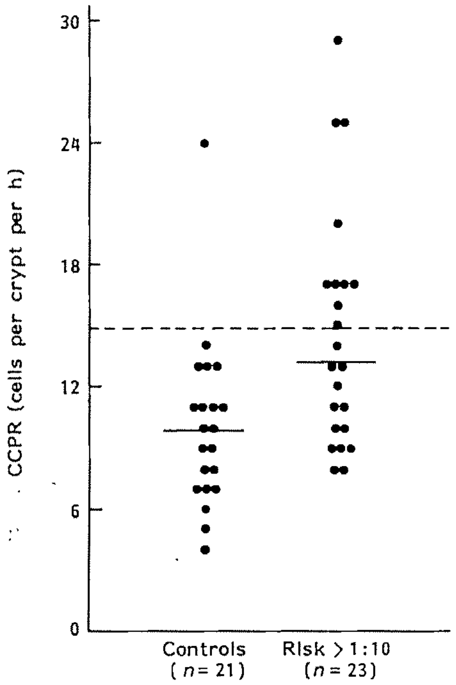

Figure 3 *Relationship between crypt cell production rate (CCPR) and high lifetime risk of colorectal cancer. Bars are medians; the dotted line indicates the 95th centile of control group data, used to define the upper limit of normal proliferation*

Discussion

Raised CCPR is related to an increased risk of colorectal cancer determined by a strong family history of the disease. In the high-risk group there was striking variation in CCPR compared with controls. Some individuals in the high-risk group had a low CCPR and there was overlap of confidence intervals with the control group. This may be explained because some individuals in the high-risk group will not have a genetic predisposition to colorectal cancer. Those at intermediate risk did not demonstrate similar variation, but the small sample size may be one explanation.

More individuals in the high-risk group expressed mucosal hyperproliferation than were calculated as the 'expected cancer phenotypes'. This increased proportion of individuals with hyperproliferation may be explained by shared environmental effects or polygenic factors, as Lovett postulated in explaining the apparent non-mendelian pattern of inheritance in her pedigrees[9]. Burt *et al.* proposed an alternative hypothesis based on a single partially penetrating autosomal dominant gene[19]. They found a greater number of individuals with adenomas in a family history group than in controls and postulated that adenomas were inherited in an autosomal dominant fashion, which would explain the familial clustering of cancers and adenomas. Fearon and Vogelstein[7] postulated transformation of flat mucosa to adenoma mediated through mucosal hyperproliferation due to a genetic defect in chromosome 5. If Burt *et al.* and Fearon and Vogelstein are correct, then the increased proportion of individuals in the high-risk group with abnormal proliferation should be expected.

No time-scale for the development of hyperproliferation is known. This study shows that transformation to a hyperproliferative state is an early one as the patients in the study group were significantly younger than controls. It is possible that the age distribution alone may explain the results, but this is not likely. One study[20], relating age and rectal mucosal proliferation in individuals shown to be free of neoplasia at colonoscopy, found a significantly lower rate of proliferation in those below the age of 50 years compared with those over 75 years. Had data from the present study followed this pattern the effect of age would have tended to manifest itself in a higher proliferation rate in the controls and lower proliferation in the younger study group. This was not the case, suggesting that other factors are acting. Deschner *et al.* described a study of young individuals at high risk of colorectal cancer and found more proliferation abnormalities in this group than in a control group of young medical students, although there was no increase in the labelling index[21].

Other *in vitro* proliferation studies using the metaphase arrest technique in humans have shown an increased CCPR associated with ulcerative colitis and adenoma formation[14,18]. All the mucosal samples were histologically verified as normal and no patient with colitis was identified in the present study. In the control group there was a single outlying CCPR of 24 cells per crypt per h, the significance of which is unclear. An adenoma may have been overlooked as Hixson *et al.* found that 14 per cent of adenomas of diameter <8 mm were missed at colonoscopy[22].

This study has shown mucosal hyperproliferation to be present in a group of individuals with a strong family history of colorectal cancer; those with mucosal hyperproliferation may warrant closer surveillance. Mucosal hyperproliferation may be used as a biomarker in trials of dietary or pharmacological intervention, with response monitored by further measurements. Additional work is needed to define the applicability of mucosal proliferation measurements as a marker for cancer risk in such individuals.

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References

1. Deschner EE, Lipkin M, Solomon C. Study of human rectal epithelial cells *in vitro*. II. ^{3}H-thymidine incorporation into polyps and adjacent mucosa. *J Natl Cancer Inst* 1966; **36**: 849–57.
2. Bleiberg M, Mainguet P, Galand P. Cell renewal in familial polyposis: comparison between polyps and adjacent healthy mucosa. *Gastroenterology* 1972; **63**: 240–5.
3. Deschner EE, Lipkin M. Proliferative patterns in colonic mucosa in familial polyposis. *Cancer* 1975; **35**: 413–18.
4. Deschner EE, Maskens AP. Significance of the labelling index and labelling distribution as kinetic parameters in colorectal mucosa of cancer patients and DMH treated animals. *Cancer* 1982; **50**: 1136–41.
5. Lipkin N, Blattner W, Gardener JE *et al.* Classification and risk assessment of individuals with familial polyposis, Gardner's syndrome and familial non-polyposis colorectal cancer from ^{3}H-thymidine labelling patterns and colonic epithelial cells. *Cancer Res* 1984; **44**: 4201–7.
6. Lipkin N, Blattner WE, Fraumeni JF, Lynch H, Deschner EE, Winawar S. Tritiated thymidine (Φ_p, Φ_h) labelling distribution as a marker for hereditary predisposition to colon cancer. *Cancer Res* 1983; **43**: 1899–904.
7. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759–67.
8. Warthin AS. Hereditary with reference to carcinoma as shown by a study of the cases examined in the pathological laboratory at the University of Michigan 1895–1913. *Arch Intern Med* 1913; **12**: 546–55.
9. Lovett E. Family studies and cancer of the colon or rectum. *Br J Surg* 1976; **63**: 13–18.
10. Houlston RS, Murday V, Harocopos C, Williams CB, Slack J. Screening and genetic counselling for relatives of patients with colorectal cancer in a family cancer clinic. *BMJ* 1990; **301**: 366–8.
11. Wright NA, Appleton DR. The metaphase arrest technique: a critical review. *Cell and Tissue Kinetics* 1980; **13**: 643–63.
12. Finney KJ, Ince P, Appleton DR, Sunter JP, Watson AJ. A comparison of crypt cell proliferation in rats on the mucosa *in vivo* and *in vitro*. *J Anat* 1986; **149**: 177–88.
13. Appleton GVN, Wheeler EE, Chalcombe DN, Williamson RCN. Validation of organ culture in colonic adaptation to surgical manipulation. *Gut* 1991; **32**: 1027–30.
14. Allan A, Bristol JB, Williamson RCN. Crypt cell production rate in ulcerative proctocolitis: differential increments in remission and relapse. *Gut* 1985; **26**: 999–1003.
15. Allan A, Jewell DP. *In vitro* model for the assessment of luminal factors on rectal mucosa. *Gut* 1983; **24**: 812–17.
16. Fireman Z, Rozen P, Fine N, Chetrit A. Reproducibility studies and effects of bowel preparation on measurements of rectal epithelial proliferation. *Cancer Lett* 1989; **45**: 59–64.
17. Pockros PJ, Foroozan P. GoLytely lavage *versus* a standard colonoscopy preparation. Effect on normal colonic histology. *Gastroenterology* 1985; **88**: 545–8.
18. Barsoum GH, Hendrickse C, Winslet M *et al.* Reduction of mucosal crypt cell proliferation in patients with colorectal adenomatous polyps by dietary calcium supplementation. *Br J Surg* 1992; **79**: 581–3.
19. Burt RW, Bishop T, Cannon LA, Dowdle MA, Lee RG, Skolnick MH. Dominant inheritance of adenomatous colonic polyps and colorectal cancer. *N Engl J Med* 1985; **312**: 1540–4.
20. Roncucci L, Ponz de Leon M, Scalmati A *et al.* The influence of age on colonic epithelial cell proliferation. *Cancer* 1988; **62**: 2373–7.
21. Deschner EE, Godblad J, Lynch HT. Rectal epithelial cell proliferation in a group of young adults. Influence of age and genetic risk. *Cancer* 1988; **61**: 2286–90.
22. Hixson LJ, Fennerty MB, Sampliner RE, Garewal HS. Prospective blinded trial of the colonoscopic miss rate of large colorectal polyps. *Gastrointest Endosc* 1991; **37**: 125–7.

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Life quality and psychological morbidity with an ileostomy

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The recent introduction of restorative proctocolectomy for the treatment of ulcerative colitis has reopened the debate about the effects of ileostomy on quality of life. This study analysed life quality and psychological morbidity in 113 patients with an ileostomy using a postal questionnaire which included questions about their opinion of the pouch operation. Of the questionnaires, 73 per cent were suitable for analysis. A total of 93 per cent of those responding were happy with the ileostomy and appeared to have adapted to a normal life with it. Some 87 per cent stated that they would keep the ileostomy in preference to an ileoanal pouch. In addition, psychological morbidity as assessed by the General Health Questionnaire occurred in only 5 per cent of patients.

Panproctocolectomy with terminal ileostomy has been the standard surgical management for ulcerative colitis for a long time. The procedure is curative and the clinical results generally believed to be excellent. The main disadvantage is that the patient is left with a permanent ileostomy incontinent of stool and gas. After the introduction of the spout ileostomy by Brooke[1] in 1952 the stomal problems of stenosis, retraction and peristomal irritation decreased markedly. Recently restorative proctocolectomy has been developed and is currently preferred to panproctocolectomy in many centres as it eliminates the need for a permanent stoma. This is an attempt to achieve normality and improve the patient's quality of life. However, the operation is not without its own problems such as sepsis, the need for revisional procedures, and worrying changes in pouch epithelium with the passage of time. Such concerns prompted reanalysis of the effects of an ileostomy on the patient's lifestyle. Previous studies have shown that patients' attitudes and lifestyles were not impaired[2–9], although others have suggested difficulties in as many as 45 per cent of cases[10,11].

It is difficult to assess quality of life because of the lack of a perfect yardstick. Patients' quality of life and the presence or absence of psychological morbidity were audited using a postal questionnaire, in conjunction with the General Health Questionnaire (GHQ 30), used for the first time in patients with an ileostomy.

Patients and methods

A questionnaire was sent to 113 patients with an ileostomy under long-term follow-up at the North Staffordshire Hospital Centre. Not all of the patients were originally operated on in this centre: some had the operation at other hospitals and then moved to the area. A postal questionnaire (available from the authors on request) was preferred to interviewing to avoid interviewer bias. The questions related to the stoma, bag emptying and changing, peristomal skin problems, dietary restrictions, leisure activity, holidays and travel, sex life, sporting activity and an assessment of satisfaction, to find out whether or not the patients were happy with the ileostomy. A final question asked the patient's view on the pouch procedure. The patients were asked whether, given the opportunity, they would have preferred an ileoanal pouch instead of the ileostomy. Details were given of frequency of bowel action by day and night, and it was stressed that more than one operation might be required to construct an ileoanal reservoir. All questions were designed so that an objective response could be given. A copy of the GHQ 30 was enclosed to assess psychiatric morbidity. This questionnaire is the 'gold standard' in screening for psychiatric disorders. It is aimed at detecting those forms of psychiatric disorder that may have relevance to a patient's medical condition, so that its focus must be on psychological components of ill-health[12]. The study used version 30, containing 30 questions, and the GHQ method of scoring, which reduces the bias associated with bimodal response scales. This method has the advantage of eliminating any errors from 'end-users' and 'middle-users'[12].

The patients who replied (32 men and 50 women) had a mean age of 52·7 (range 17–91) years, mean age at time of surgery of 40·1 (range 12–75) years and mean duration with the ileostomy of 12·8 (range 1–44) years.

Results

Questionnaires were returned by 82 patients, a response rate of 73 per cent. Only 39 patients answered specifically the 'indication for surgery' question: 26 had had surgery for ulcerative colitis and 13 for Crohn's disease.

The mean daily frequency of bag emptying was 3·6 (range 2–8). The mean weekly frequency of bag change was 1·7 (range 1–6). Only 5 per cent of patients reported a need to empty or change the bag during the night. Some 35 per cent of patients reported that the bag leaked once a week or once a month.

The ileostomy had undergone retraction or protrusion episodes at some time in 36 patients. Peristomal skin irritation had occurred at some point in 58 (74 per cent) of patients but only in nine (11 per cent) of the total number of patients was it weekly and in 16 (20 per cent) monthly. The remainder reported that skin irritation episodes were annual or even less frequent. Twenty patients (26 per cent) reported never having any peristomal skin irritation.

Medication was required to control the ileostomy effluent in 32 per cent of patients. Ten (12 per cent) used the medication permanently and four patients (5 per cent) employed more than one preparation for this purpose. The preparations used were codeine phosphate, diphenoxylate and loperamide.

Dietary restrictions were common: 40 per cent of patients avoided particular food to prevent excessive gas and smell production, and 35 per cent did the same to avoid excessive ileostomy effluent. A total of 21 patients (26 per cent) restricted food intake before long journeys.

The patient's work, social and leisure activities were affected in a substantial number of cases (*Table 1*). Thirteen changed their job as a result of having the stoma. Twenty-five patients (30 per cent) played sport before surgery and three stopped sporting activities as a direct result of the stoma. Only 17 patients (21 per cent) reported that the ileostomy affected their leisure activities. Housework and gardening taken together were affected in 28 (34 per cent), but in 15 (18 per cent) these effects were mild. Holidays were affected in 30 (37 per cent) of patients, only mildly in 17 (21 per cent). Sex life was affected in 34 cases (46 per cent), with mild effects reported by 16 (22 per cent).

The patients were generally satisfied with the ileostomy, with 76 (93 per cent) happy with the stoma. Answers to this question varied from 'As happy as one could be' to 'It is wonderful, we should have been born with one!'. Most patients (65;

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Table 1 *Lifestyle activities affected by the ileostomy*

	No. of patients	Total no. of answers
Change in employment‡		
Yes	13 (16)	80
No	67 (84)	
Sport affected		
Yes	3 (12)	25
No	22 (88)	
Leisure activities affected		
Yes	17 (21)	81
No	64 (79)	
Housework and gardening affected		
Severely	3 (4)	82
Moderately	10 (12)	
Mildly	15 (18)	
No change	42 (51)	
Improvement	12 (15)	
Holidays affected		
Severely	1 (1)	81
Moderately	12 (15)	
Mildly	17 (21)	
No change	34 (42)	
Improvement	17 (21)	
Sex life affected		
Severely	10 (14)	74
Moderately	8 (11)	
Mildly	16 (22)	
No change	35 (47)	
Improvement	5 (7)	

Values in parentheses are percentages

87 per cent) indicated that they would not have preferred an ileoanal pouch to the ileostomy.

In the GHQ a threshold score of 4 out of 5 is taken as an indication of significant clinical disturbance[12]. Four patients with an ileostomy (5 per cent) exceeded this threshold, indicating significant psychiatric morbidity. Two patients were on the borderline, scoring 3·6 and 3·8. The mean score was 0·58.

Discussion

It seems that patients with an ileostomy generally cope well; indeed 93 per cent were happy with the stoma. McLeod *et al.*[13] found that the restrictions in lifestyle that were encountered by some were fewer than those present before operation.

Peristomal skin irritation occurred in 74 per cent of patients at some time after operation. This was the most common problem in the present series. Other studies confirm these findings, peristomal skin irritation being found in 49–74 per cent of patients[3,13–15]. Some 26–40 per cent of patients in the present study applied some form of dietary restriction to avoid excessive odour or decrease ileostomy effluent. This was only mild self-imposed restriction and no specific diet was mentioned, but it seems that trial and error established which particular items needed to be avoided. Sport and leisure activities were restricted in only a minority of patients in this study, although 34 and 37 per cent reported that they were affected when asked about housework and holidays respectively. Overall, 20 per cent reported mild restrictions of holidays and housework, and only four were 'severely affected'; the rest were in the 'moderate' category. Morbidity occurred with respect to sexual activity: 14 per cent of patients were severely affected and a total of 46 per cent adversely affected to some degree. Pemberton *et al.*[15] reported that 30 per cent of patients with a Brooke ileostomy had sexual limitations, compared with 13 per cent of those with ileal pouch–anal anastomosis. A change of employment was necessary for 16 per cent of the present patients; a similar figure was reported in a previous study[13]. The present authors were impressed to find that psychiatric morbidity occurred in only 5 per cent of patients with an ileostomy in the present series. In the Cleveland Clinic study[13], using a different method to assess psychological morbidity, 10 per cent of patients were found to have experienced negative feelings from employers, friends and family because of the ileostomy and 22 per cent felt they were less attractive physically with a stoma.

What is interesting and encouraging is that almost 20 per cent of the present patients reported improvement in a variety of lifestyle activities and this could be explained only by the general improvement in health after overcoming severe and debilitating illness. We feel that panproctocolectomy with ileostomy still offers patients a good quality of life, and its value must not be underestimated. The majority of patients appear to have adapted well to their new life with a stoma without major psychological morbidity. Most would be reluctant to consider conversion to an ileoanal pouch. This question was asked not to compare patients with an ileostomy with those with a pouch, or to undermine pouch work, but simply to find the views of patients after living with a stoma for a long time. In the Mayo Clinic study[15], the overall satisfaction with results of the operation was 93 per cent for Brooke ileostomy and 95 per cent for ileal pouch–anal anastomosis. In that study, 98 per cent of patients with a Brooke ileostomy and 94 per cent of those with ileoanal pouches returned to work or school after operation.

Since it is now highly unlikely that prospective randomized trials could be mounted to compare these procedures, surgeons will have to rely on audit techniques such as those used in this report to evaluate results. A large national study of patients with an ileoanal pouch in whom such methods have been used is now required.

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References

1. Brooke BN. Management of ileostomy including its complications. *Lancet* 1952; ii: 102–4.
2. Roy PH, Sauer WG, Beahrs OH, Farrow GM. Experience with ileostomies: evaluation of long-term rehabilitation in 497 patients. *Am J Surg* 1970; **119**: 77–86.
3. Morowitz DA, Kirsner JB. Ileostomy in ulcerative colitis: a questionnaire study of 1803 patients. *Am J Surg* 1981; **141**: 370–5.
4. Brooke BN. Outcome of surgery for ulcerative colitis. *Lancet* 1956; ii: 532–6.
5. Bone J, Sorensen FH. Life with a conventional ileostomy. *Dis Colon Rectum* 1974; **17**: 194–9.
6. Watts JMcK, DeDombal FT, Goligher JC. Long-term complications and prognosis following major surgery for ulcerative colitis. *Br J Surg* 1966; **53**: 1014–23.
7. Wilson E. The rehabilitation of patients with an ileostomy established for ulcerative colitis. *Med J Aust* 1964; **1**: 842–5.
8. Rhodes JB, Kirsner JB. The early and late course of patients with ulcerative colitis after ileostomy and colectomy. *Surg Gynecol Obstet* 1965; **121**: 1303–14.
9. Hill GL. *Ileostomy: Surgery, Physiology and Management*. New York: Grune and Stratton, 1976.
10. Druss RG, O'Connor JF, Prudden JF, Stern O. Physiologic response to colectomy. *Arch Gen Psychiatry* 1968; **18**: 53–9.
11. Failes D. The Kock continent ileostomy: a preliminary report. *Aust N Z J Surg* 1976; **46**: 125–30.
12. Goldberg D. *The Detection of Psychiatric Illness by Questionnaire*. Maudsley monograph 21. London: Oxford University Press, 1972.
13. McLeod RS, Lavery IC, Leatherman JR *et al.* Patient evaluation of the conventional ileostomy. *Dis Colon Rectum* 1985; **28**: 152–4.
14. Biermann HJ, Tocker AM, Tocker LR. Statistical survey of problems in patients with colostomy or ileostomy. *Am J Surg* 1966; **112**: 647–9.
15. Pemberton JH, Phillips SF, Ready RR, Zinsmeister AR, Beahrs OH. Quality of life after Brooke ileostomy and ileal pouch–anal anastomosis. *Ann Surg* 1989; **209**: 620–8.

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Ulcerative colitis in familial adenomatous polyposis

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Pouchitis occurs in 5–30 per cent of patients following restorative proctocolectomy for ulcerative colitis, but is very rare after similar surgery in patients with familial adenomatous polyposis (FAP)[1]. The aetiology of pouchitis remains unknown, but some have suspected an aetiological relation with ulcerative colitis. For this view to be tenable, there must be an explanation for the occasional well documented case of pouchitis in a patient with FAP[2]. Two patients with FAP have been encountered who have also had a diagnosis of ulcerative colitis. This association might explain the occasional case of pouchitis in a patient with FAP and still allow the aetiology of pouchitis and ulcerative colitis to be closely linked.

Case reports

Patient 1

A 23-year-old woman from a known polyposis family underwent colectomy and ileorectal anastomosis. The resected specimen contained 1059 adenomatous polyps. The patient also had multiple cysts and congenital hypertrophy of the retinal pigment epithelium.

Initial postoperative bowel frequency was two to three times daily with no urgency. Some 19 months after operation she developed bloody diarrhoea, up to seven times daily, and abdominal pain. Sigmoidoscopy 1 month later revealed a friable bleeding mucosa, biopsy of which showed features of active ulcerative colitis with a villiform architecture, crypt distortion, goblet cell depletion and occasional small crypt abscesses. Stool culture did not reveal any pathogens. The patient was successfully treated with tablets of mesalazine and hydrocortisone enemas (Colifoam; Stafford–Miller, Welwyn Garden City, UK).

Patient 2

A 22-year-old man presented with a 10-month history of diarrhoea and recent passage of blood rectally. Endoscopy showed a moderately differentiated adenocarcinoma of the rectum. Anterior resection revealed a Dukes' C adenocarcinoma with nine synchronous adenomatous polyps. Subsequent colonoscopy showed multiple polyps and a diagnosis of FAP was made. Colectomy with ileostomy was performed and the rectal stump oversewn. Histological examination showed multiple tubular adenomas scattered throughout the colon; in the intervening mucosa there was active ulcerative colitis with distortion and branching of the crypt architecture with crypt abscesses and goblet cell mucin depletion. There was a diffuse chronic inflammatory cell infiltrate in the lamina propria and no granulomas were seen. A diagnosis of FAP with ulcerative colitis was made.

Discussion

These two cases clearly demonstrate the unusual concurrence of FAP and ulcerative colitis. The single well documented report of a patient with FAP and pouchitis[2] has previously raised some doubt as to an aetiological association between pouchitis and ulcerative colitis, but no comment was made on the histological appearance of the resected colon in that case. It is possible that this case of pouchitis in FAP arose in a patient similar to those in the present report. Taken together, these three cases thereby reinforce rather than contradict the probable aetiological relation of ulcerative colitis to pouchitis.

References

1. Scott AD, Phillips RKS. Ileitis and pouchitis after colectomy for ulcerative colitis. *Br J Surg* 1989; 76: 668–9.
2. Kmiot WA, Williams MR, Keighley MRB. Pouchitis following colectomy and ileal reservoir construction for familial adenomatous polyposis. *Br J Surg* 1990; 77: 1283.

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Screening practice for familial adenomatous polyposis: the potential for regional registers

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Existing screening practice for familial adenomatous polyposis (FAP) was evaluated in 47 families with FAP notified to the West Midlands Polyposis Register between February 1988 and July 1990. Of these 269 individuals, 107 were known to be affected and 162 were at 50 per cent prior risk of developing FAP; 35 deceased affected individuals from living generations were included in the analysis. Of 105 individuals in the at-risk group aged between 12 and 40 years, only 55 (52 per cent) were under follow-up by bowel examination. Thirty-seven affected individuals had developed colorectal carcinoma before diagnosis; the incidence was three of 51 (6 per cent) in those diagnosed through screening compared with 34 of 53 (64 per cent) in the unscreened group ($P < 0{\cdot}001$)*. A total of 28 individuals (26 per cent of the FAP population) died from advanced colorectal carcinoma; all were from the unscreened population. In 22 (59 per cent) of the cases of colorectal carcinoma and 17 (61 per cent) of the deaths from advanced colorectal cancer there was a positive family history of FAP; these tumours were therefore potentially preventable through screening and prophylactic surgery. Since establishing the register the median age at diagnosis of the affected patients has been reduced from 32 to 23 years* ($P = 0{\cdot}0004$) *and the incidence of colorectal cancer has fallen from 35 to 14 per cent* ($P < 0{\cdot}05$)*. It is concluded that by providing more comprehensive case ascertainment a regional register can have a dramatic effect on this largely preventable form of colorectal cancer. Regional registers are recommended as an essential component of screening for this disease.*

Familial adenomatous polyposis (FAP) is an inherited condition, passed on in an autosomal dominant fashion, that when left untreated leads inevitably to the development of colorectal carcinoma[1]. Although the spontaneous mutation rate has been estimated[1–3] as up to 40 per cent, colorectal carcinoma should be entirely preventable in at least 60 per cent of cases through effective family screening. FAP is known to have almost complete penetrance, with all affected individuals developing widespread adenomatous polyps in the colon and rectum[1,4]. All affected family members will go on to develop colorectal carcinoma, usually by the age of 35–40 years[1]. As is the case with most inherited cancers, an increased incidence of other malignancies has been shown in FAP including periampullary carcinoma[5,6], thyroid carcinoma[7], hepatoblastoma[8] and medulloblastoma[9]; potentially life-threatening desmoid tumours also occur in up to 10 per cent of cases[10,11]. The inevitability of colorectal carcinoma and its early age of onset, however, make this the most important disease manifestation.

The pathognomonic feature of FAP is the development of hundreds, often thousands, of adenomatous polyps in the colon and rectum[3]. These usually appear by the age of 15–20 years, but may not be visible until as late as 38 years of age[1]. Because the development of adenomatous polyps always precedes colorectal carcinoma, this feature has been used as a diagnostic marker for over half a century[12]. The only effective treatment currently available is prophylactic colectomy[13], the success of which is largely dependent on adequate screening of all family members who are at risk to identify new cases before the development of carcinoma. Because the age at which colorectal polyps develop is variable, screening by repeated bowel examination is necessary from puberty until at least 40 years of age before a family member can be considered unaffected[1,6,14].

In 1988 a FAP interest group was started in the West Midlands with the purpose of establishing a regional register of families. Its aims included the assessment of existing screening practice and the introduction of adjuvant screening techniques. This paper reports on the pre-existing screening and treatment practices in 47 families with FAP notified to the regional register up to July 1990. To evaluate its impact, age at diagnosis and incidence of colorectal cancer are also reported subsequent to the establishment of the register.

Patients and methods

The study population was limited to families living in the West Midlands, regardless of where individual family members had undergone treatment. The region comprises 22 health districts and has a population of 5·5 million. The FAP interest group was established through collaboration between Birmingham University Department of Surgery and the West Midlands Regional Department of Clinical Genetics. The register was publicized through local surgery and gastroenterology meetings and also through personal contacts with departments around the region. The interest group also funded a research fellow (D.G.M.) to help coordinate development of the register.

All index cases were notified to the register from consultants in the West Midlands region, who gave permission to contact patients. The index case was then contacted and visited, usually at home, by specialist genetics clinic nurses. Such individuals were informed of the purpose of the register and, with the family's permission, a pedigree was constructed. The general practitioners and consultants involved with the other family members were then contacted to obtain permission to approach them and arrange for appropriate investigations. Pedigrees were confirmed by visiting other branches of the family; for the extended family, this often necessitated involving other regional genetics services. At this point the histology reports of the index cases and any key individuals in the pedigree were requested. Where the diagnosis remained in doubt, available specimens and colonic tissue sections were

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reviewed at the local hospital; in three such cases the sections were forwarded for a second opinion before a diagnosis was reached. Diagnosis depended on identifying more than 100 colorectal polyps, several of which had to be confirmed as adenomas.

The families were then invited to attend a genetic counselling clinic. Initially this occurred in genetics clinics in local hospitals but in March 1990 a combined ophthalmic and genetics clinic was established to which all families were invited to attend for a single visit. At this visit the genetic implications of the condition were explained and the necessary screening procedures outlined. In addition, a venous blood sample was taken for predictive diagnosis[15–17] using polymorphic probes linked to the causative gene on chromosome 5. Individuals also underwent an ophthalmic examination for congenital hypertrophy of the retinal pigment epithelium[18,19].

Patient details were collated from the patients themselves and family members, and confirmed from medical records where available. Although full medical records had often been destroyed, histology reports were invariably retained, enabling the nature of the operation and the findings to be corroborated.

Information was stored on all individuals who were affected or born with a 50 per cent risk of developing the disease. Any results from pedigree data, eye tests or DNA probe analyses were forwarded to the consultants and general practitioners concerned.

Statistical analysis on continuous data was performed using the two-tailed Mann–Whitney U test and on categorical data by the χ^2 test with Yates' correction. Significance was assumed at $P < 0.05$.

Results

Pedigree data

A total of 54 index cases were notified to the register in the first 2 years. Seven cases and their respective families proved not to have histological evidence of FAP; two pedigrees had a Lynch type II pattern of inheritance[20], one pedigree had juvenile polyposis, two others a Lynch type I pattern[20] and in two families the pattern of inheritance was uncertain. Only the remaining 47 pedigrees, involving 269 individuals, were included in the study. The disease status of the individuals from these families is shown in *Table 1*.

The patients on the register were under the care of 41 consultants in 27 hospitals throughout the West Midlands and 20 family members were being followed up in five outside regions. The register did not influence the number of consultants involved because family members visited local hospitals for bowel screening and were invariably referred to consultants already dealing with screening for FAP.

At-risk individuals

There were 162 living individuals with a known affected parent who were therefore at 50 per cent prior risk of developing the disease; 48 were aged ⩽12 years at the time of notification and considered too young for screening. A further nine were aged over 40 years and had undergone a recent bowel examination; these were considered at sufficiently low risk to exclude from further screening. The remaining 105 individuals were at the appropriate age for screening. However, only 55 (52 per cent) of these were under follow-up.

Although previously many cases underwent barium enema at diagnosis, this practice has been replaced in the past decade by colonoscopy. Of the 55 individuals being screened, only four (7 per cent) had undergone barium enema examination in the past 5 years, 23 (42 per cent) either rigid or flexible sigmoidoscopy and 28 (51 per cent) colonoscopy.

Affected patients

A total of 107 affected patients were identified from the 47 proven FAP pedigrees; 35 deceased individuals from living generations were included. The affected family members had been treated by 34 consultants at 24 hospitals in the West Midlands and at a further five centres outside this area. The type of operation performed is shown in *Table 2*.

In addition to the carcinomas found at diagnosis, four of 48 patients (8 per cent) developed tumours in the rectal stump after subtotal colectomy with ileorectal anastomosis; one also had a colonic carcinoma present at initial operation.

Method of diagnosis

Of the 107 affected cases, 20 (19 per cent) were isolated (potential spontaneous mutations) with no clear history of an affected parent or siblings; this group could not have been identified through family screening. Of the others (pedigree cases) either a first-degree relative had already been diagnosed or one parent had developed colonic carcinoma before 45 years of age, indicating the likely presence of inherited disease. These

Table 1 *Details of patients on the West Midlands Polyposis Register*

	M		F		Total	
	No.	Mean age (years)*	No.	Mean age (years)*	No.	Mean (range) age (years)*
Affected						
Deceased	20	37	15	41	35	39 (20–59)
Living	36	29	36	28	72	28 (0–58)
At 50% prior risk	73	21	89	19	162	20 (0–69)
Total	129		140		269	

*At death in deceased affected individuals, at diagnosis in living affected individuals and at time of referral to the register in those at 50 per cent prior risk

Table 2 *Details of operations performed on 107 patients with familial adenomatous polyposis*

Operation	Patients	Consultants	Hospitals	Median (range) year	Patients with colorectal cancer
Palliative treatment	4	4	4	1977 (1975–1979)	4
Hemicolectomy	4	4	4	1982 (1968–1989)	4
Subtotal colectomy with ileorectal anastomosis	48	22	17	1983 (1963–1990)	18*
Panproctocolectomy with ileostomy	30	19	16	1983 (1963–1990)	13
Proctocolectomy with ileoanal pouch	18	5	5	1988 (1982–1990)	1
Unknown	3	—	—	— —	0
Total	107	41	30	1984 (1963–1990)	40

*Four cases of rectal carcinoma occurred in the rectum remaining after operation

87 pedigree cases were categorized by initial reason for investigation: in 51 (59 per cent) this was because of call-up through family screening and in 36 (41 per cent) entirely because of the onset of bowel symptoms.

A total of 37 patients had at least one colorectal carcinoma found at the time of diagnosis: 15 of 20 (75 per cent) isolated cases and 22 of 87 (25 per cent) pedigree cases. These 22 represent potentially preventable cancers. There were 28 deaths directly attributable to disseminated colonic carcinoma, of which 11 occurred in isolated cases. The remaining 17 were in pedigree families, representing a mortality rate of 20 per cent; these deaths were potentially preventable through more comprehensive family screening.

In addition to the 28 deaths attributed to colorectal carcinoma there were seven from other causes: two from road traffic accidents, one pulmonary embolus, one leukaemia, one testicular cancer and two probable ampullary carcinoma.

The high proportion of symptomatic patients was associated with a delay in diagnosis after the expected age at onset of adenomatous polyps. The median age at diagnosis of polyposis in the pedigree group was 29 (range 8–58) years, a mean of 13 years after the expected mean age at onset of adenomatous polyps ($P < 0{\cdot}001$) (*Figure 1*).

The mean age at diagnosis of colorectal carcinoma ($n = 40$) was 31 (range 18–58) years. Comparison between patients with FAP diagnosed through screening and those diagnosed because of symptoms revealed a 15-year difference in the mean age at diagnosis ($P < 0{\cdot}001$) and a tenfold reduction in the incidence of colorectal carcinomas found at the time of diagnosis ($\chi^2 = 36{\cdot}0$, 1 d.f., $P < 0{\cdot}001$) (*Table 3*). Moreover, the Dukes' classification of the cancers was far more advanced in the symptomatic group (*Table 3*). All deaths attributable to advanced colorectal carcinoma occurred in symptomatic individuals.

Impact of the family register

The mean age at diagnosis of the affected population was calculated before and after establishing the register. The age and date of diagnosis was ascertained in 124 affected cases known to the register from 1961 up to the end of 1991. From 1961 to 1987 the mean age at diagnosis (86 cases) was 33 (median 32) years and did not alter significantly during that time. Since 1988, however, the mean age has fallen steadily from 27 (median 25) years in 1988 to a low of 20 (median 18) years in 1990, rising slightly to 23 (median 20) years in 1991. This reduction in the age at diagnosis since introduction of the family register is significant ($P = 0{\cdot}0004$). The fall in the age at diagnosis was accompanied by a predictable rise in the number of cases being diagnosed, from a previous peak of 6 per year to 12 annually for the first 2 years of the register.

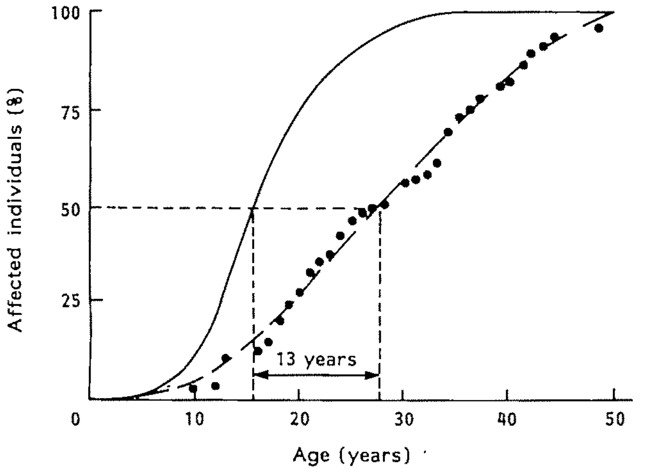

Figure 1 *Comparison of expected age at onset of polyps (——) with actual age at diagnosis (●) in 87 pedigree cases. (Data for onset of polyps from Murday and Slack*[21]*)*

A further five cases (14 per cent) of colorectal cancer have been diagnosed since the register was established (two were index cases) compared with 37 (35 per cent) previously ($\chi^2 = 4{\cdot}9$, 1 d.f., $P < 0{\cdot}05$).

Discussion

The development of a regional register of families with FAP has, for the first time, enabled screening and treatment for this disease to be reviewed in the West Midlands.

The population of this area is approximately 5·5 million. FAP has a reported incidence[1,22–26] of 0·4–1·3 per 10 000 and a point prevalence[1,26] of about 1 per 35 000. The most complete data come from Scandinavia where population-based registers have been established for more than a decade. There are 70 000 births a year in the West Midlands region, so about 150 living affected individuals and a further 300 with a prior 50 per cent risk would be expected in the population; this is over twice the number so far identified. Incomplete ascertainment is due in part to incomplete notification of families. Other non-ascertained cases will include undiagnosed new mutations, and treated individuals in whom the diagnosis was missed.

Accuracy of diagnosis is of paramount importance if correct advice for family screening is to be given. In the present series, seven families did not have evidence of FAP and in these cases alternative screening procedures were recommended. This becomes increasingly important when adjuvant screening measures, using linked polymorphic DNA probes or indirect ophthalmoscopy, are undertaken[17,19,26,27].

The low screening rate (55 per cent) among the population at risk is likely to have various causes; the patients' fear of repeated bowel examinations and their findings undoubtedly plays a part. However, a significant number of this population were unaware of the risk to themselves or their relatives. The large number of consultants and hospitals involved in treating the families compounds the problems. More than one-quarter of the general surgeons in the region are involved with treatment and follow-up of the families on the register, and other family members may live outside the region and wish to be treated locally. This makes the collating and updating of pedigrees difficult for isolated clinicians. Coordinating screening through a regional register overcomes this and so would be expected to improve ascertainment.

Despite the low incidence of proximal carcinomas developing without evidence of rectal polyposis, the use of flexible colonoscopy has increased in recent years. In three major series all patients with FAP with colorectal carcinoma

Table 3 *Comparison of patients identified by bowel screening with those investigated because of bowel symptoms*

Method of identification	M	F	Total	Mean (range) age at diagnosis (years)	Dukes' classification A	B	C	'D'	Unknown	Multiple	Patients with colorectal cancer
Screening	25	26	51	23·6 (10–48)	1	1	0	0	1	1	3
Symptoms	28	25	53	38·5 (12–58)	0	10	13	5	6	7	34
Unknown	2	1	3	— —	—	—	—	—	—	—	0
Total	55	52	107		1	11	13	5	7	8	37

had rectal polyps at the time of diagnosis[1,3,4] and the present findings support this. Occasional cases of proximal carcinomas occurring without overt rectal polyposis have been reported[28], but sigmoidoscopy, particularly if combined with rectal biopsy for microadenoma, should be sufficient for screening families with FAP.

The nature of the operation performed in affected patients has changed considerably over the past 10 years (*Table 2*), with panproctocolectomy increasingly being replaced by restorative proctocolectomy. The low incidence of colorectal cancer in patients undergoing restorative proctocolectomy reflects the reluctance to perform this procedure in the presence of colorectal carcinoma. There is also a reluctance to perform subtotal colectomy in the presence of widespread rectal polyps[29]. Early diagnosis is therefore of paramount importance for patients to be offered these alternative operations.

Late diagnosis, particularly after the onset of symptoms, was associated with an unacceptably high incidence of colorectal carcinoma in the present patients: 34 of 53 (64 per cent) of the unscreened population. Furthermore, the majority of these tumours were advanced at the time of diagnosis (*Table 3*), and the cancer-related mortality rate in unscreened cases was 82 per cent. In contrast, only three carcinomas were found in the screened population and all patients underwent curative surgery.

Because of improvements in diagnostic and therapeutic techniques, the exact long-term impact of the register on colorectal cancer morbidity and mortality rates in these families will never be entirely clear. The immediate impact of this regional initiative is, however, already apparent, with a rise in the number of cases diagnosed and a reduction of 9 years in the mean age at diagnosis. These improvements have been mirrored by a fall in the incidence of colorectal cancer from 35 to 14 per cent of the affected population at the time of diagnosis.

The impact of the register also includes: the tracing of 50 at-risk cases previously unknown or lost to follow-up to be contacted for bowel screening; counselling of the parents of 44 children at risk for FAP; increasing awareness of the condition, among both clinicians and affected families; and instituting predictive testing using indirect ophthalmoscopy and linked polymorphic probes.

Although this is a selected population, including only those families known to the register, the lowering of the age at diagnosis and reduction in the associated incidence of colorectal cancer serve to indicate the importance of family registration as an aid to screening for FAP.

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References

1. Bulow S. Familial adenomatous polyposis. *Danish Medical Journal* 1987; **34**: 1–15.
2. Utsunomiya J, Iwama T. Adenomatous coli in Japan. In: Winawer J, Schottenfeld D, Sherlock P, eds. *Colorectal Cancer: Prevention, Epidemiology, and Screening*. New York: Raven Press, 1980.
3. Bussey HJR. *Familial Polyposis Coli: Family Studies, Histopathology, Differential Diagnosis and Results of Treatment*. Baltimore: Johns Hopkins University Press, 1975.
4. Alm T, Lieznerski G. The intestinal polyposes. *Baillieres Clin Gastroenterol* 1973; **2**: 577–602.
5. Jagelman DG, De Cosse JJ, Bussey HJR. Upper gastrointestinal cancers in familial adenomatous polyposis. *Lancet* 1988; **i**: 1149–51.
6. Alm T. Hereditary adenomatosis of the colon and rectum. In: Lynch HT, ed. *Colon Cancer Genetics*. New York: Van-Nostrand Reinhold, 1984.
7. Plail RO, Glazer G, Thomson JPS, Bussey HJR. Adenomatous polyposis. An association with carcinoma of the thyroid. *Br J Surg* 1987; **74**: 377–80.
8. Kingston JE, Herbert A, Draper GJ, Mann JR. Association between hepatoblastoma and polyposis coli. *Arch Dis Child* 1983; **91**: 916–25.
9. Kropilac M, Jagelman DG, Fazio DW, Lavery IL, McGannon E. Brain tumours in familial adenomatous polyposis. *Dis Colon Rectum* 1989; **32**: 778–82.
10. Jarvinen HJ. Desmoid disease as part of familial adenomatous polyposis coli. *Acta Chirurgica Scandinavica* 1987; **153**: 379–83.
11. Klemmer S, Pascoe L, De Cosse JJ. Occurrence of desmoids in patients with familial adenomatous polyposis of the colon. *Am J Med Genet* 1987; **28**: 385–91.
12. Lockhart-Mummery P. Cancer and heredity. *Lancet* 1925; **i**: 427–9.
13. Jarvinen HJ. Time and type of prophylactic surgery for familial adenomatous coli. *Ann Surg* 1985; **202**: 93–7.
14. Vasen HFA, Griffioen G, Offerhaus GJA *et al.* The value of screening and central registration of families with familial adenomatous polyposis. *Dis Colon Rectum* 1990; **33**: 227–30.
15. Bodmer WF, Bailey CJ, Bodmer J *et al.* Localisation of the gene for familial adenomatous polyposis within a small region of chromosome 5. *Nature* 1987; **328**: 614–16.
16. Dunlop MG, Wyllie AH, Steel CM, Piris J, Evans HJ. Linked markers for presymptomatic diagnosis of familial adenomatous polyposis. *Lancet* 1991; **337**: 313–16.
17. Macdonald F, Morton D, Rhindl M *et al.* The application of linked polymorphic probes in presymptomatic diagnosis of familial adenomatous polyposis. A population-based study. *BMJ* 1992 (in press).
18. Chapman PD, Church W, Burn J, Gunn A. Congenital hypertrophy of the retinal pigment epithelium: a sign of familial adenomatous polyposis. *BMJ* 1989; **289**: 353–4.
19. Morton D, Gibson J, Macdonald F *et al.* Role of congenital hypertrophy of the retinal pigment epithelium in the predictive diagnosis of familial adenomatous polyposis. *Br J Surg* 1992; **79**: 689–93.
20. Lynch HT, Kimberling W, Albano WA *et al.* Hereditary nonpolyposis colorectal cancer. *Cancer* 1985; **56**: 934–8.
21. Murday V, Slack J. Inherited disorders associated with colorectal cancer. *Cancer Surv* 1989; **8**: 139–57.
22. Reed TE, Neale JV. A genetic study of multiple polyposis of the colon. *Am J Hum Genet* 1955; **7**: 236–63.
23. Jarvinen HJ, Husa A, Aukee S, Laitinen S, Matikainen M, Havia T. Finnish Registry for familial adenomatous coli. *Scand J Gastroenterol* 1984; **19**: 941–6.
24. Bower C, Levitt S, Francis S. The Western Australian Familial Polyposis Registry. *Med J Aust* 1989; **151**: 557–60.
25. Veale AMO. *Intestinal Polyposis*. Cambridge: Cambridge University Press, 1965.
26. Burn J, Chapman P, Delhanty J *et al.* The UK Northern Region genetic register for familial adenomatous polyposis coli: use of age of onset, congenital hypertrophy of the retinal pigment epithelium and DNA markers in risk calculations. *J Med Genet* 1991; **28**: 289–96.
27. Houlston R, Slack J, Murday V. Risk estimates for screening adenomatous polyposis coli. *Lancet* 1990; **335**: 484 (Letter).
28. Bradburn DM, Gunn A, Hastings A, Shepherd NA, Chapman PD, Burn J. Histological detection of microadenomas in the diagnosis of familial adenomatous polyposis. *Br J Surg* 1991; **78**: 1394–5.
29. Moertel CG, Hill JR, Adson MA. Management of multiple polyposis of the large bowel. *Cancer* 1971; **28**: 160–4.

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Internal anal sphincter dysfunction in neurogenic faecal incontinence

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Forty-eight patients of median age 57 years with neurogenic faecal incontinence and 44 normal subjects of median age 51 years underwent fine-wire anal sphincter electromyography and anal manometry. The median (interquartile range (i.q.r.)) internal anal sphincter (IAS) electromyogram frequency was 0·26 (0·21–0·32) Hz for patients with faecal incontinence and 0·44 (0·31–0·55) Hz for controls ($P < 0{\cdot}01$). *The median (i.q.r.) ambulatory resting pressure was 48 (34–68) cmH$_2$O for patients and 86 (72–102) cmH$_2$O for controls* ($P < 0{\cdot}01$) *and median (i.q.r.) frequency of transient IAS relaxations 9 (7–12) and 4 (3–7) per h respectively* ($P < 0{\cdot}05$). *Mid-anal pressure fell to a greater extent in patients with incontinence during these episodes of transient IAS relaxation. Rectal pressure during such relaxation did not exceed mid-anal canal pressure in controls; for the patient group, rectal pressure increased during relaxation and exceeded mid-anal canal pressure in 36 cases. Frequent abnormal episodes of IAS relaxation may cause occult faecal leakage in patients with neurogenic faecal incontinence.*

Frequent episodes of transient internal anal sphincter (IAS) relaxation have been described in patients with neurogenic faecal incontinence[1]. A recent laboratory-based study described such episodes in 18 per cent of patients with incontinence[2]. To elucidate the pathophysiology of IAS dysfunction in faecal incontinence, the relationship between IAS electromyogram (EMG) activity and ambulatory anal pressure was assessed using a computerized system.

Patients and methods

Forty-eight patients (median age 57 (range 32–86) years; 42 women) with neurogenic faecal incontinence and 44 normal controls (median age 51 (range 25–81) years; 32 women) were studied. All patients were incontinent of flatus daily, incontinent of liquid and solid stool at least once per week and used incontinence pads daily. All the women in the incontinent group had an obstetric history with a median of 3 (range 2–11) vaginal deliveries; 17 of the normal controls had an obstetric history with a median of 2 (range 0–4) vaginal deliveries (three episiotomies).

Fine-wire electromyography was carried out using bared and barbed Teflon (Du Pont, Stevenage, UK)-coated stainless steel wires (0·15 mm in diameter) on the IAS, external anal sphincter (EAS) and puborectalis muscle. The patient was placed in the left lateral position and an intradermal bleb of 0·5 per cent lignocaine infiltrated into the anal skin before introduction of the wires using a 21-G needle. The wires were connected to a portable computer within the ambulatory recorder (Gaeltec, Isle of Skye, UK). The amplifier was gated into one low-frequency channel (< 10 Hz) to record IAS EMG activity and two high-frequency channels (10–1000 Hz) to record the high-frequency EAS and puborectalis activity. Recordings of anorectal pressure were simultaneously obtained using four microtransducers mounted on a probe 3 mm in diameter. The pressure transducers were located at 2, 6, 12 and 14 cm from the tip of the probe. The pressure probe was attached by an adaptor to the ambulatory recorder to allow for integrated EMG–pressure recordings. The recorder sampled each EMG and manometric channel 4 times per s throughout the recording, which allowed all IAS activity to be recorded.

The subject was allowed home and a diary kept of events including passage of flatus, defaecation and micturition. An event button facility was available on the recorder to correlate the recording with the event in the diary. The median recording time was 8 (range 3–17) h. After completion of the recording, information on the ambulatory recorder was loaded on to a computer terminal (Archimedes Taxan 410; Acorn Computers, Cambridge, UK) to be stored on a floppy or hard disc facility.

IAS EMG frequency and resting anal pressure were analysed by two observers and no significant interobserver variation was noted.

Results are presented as median (interquartile range (i.q.r.)). Statistical analysis was performed using the Mann–Whitney U test unless otherwise stated. Data from the first hour of recording were ignored to exclude residual influence of the local anaesthetic on sphincter function.

Results

Controls

The median (range) age of men (45 (28–71) years) and women (54 (25–81) years) in the control group was not significantly different ($P > 0{\cdot}1$). There was no significant correlation between median (i.q.r.) IAS EMG frequency and age ($P > 0{\cdot}3$) or sex (men, 0·44 (0·38–0·46) Hz; women, 0·44 (0·36–0·55) Hz) ($P > 0{\cdot}1$). Because no correlation was found for age and sex, all control subjects were compared. No significant sex difference was demonstrated for median (i.q.r.) resting anal pressure (men, 90 (77–102) cmH$_2$O; women, 84 (72–99) cmH$_2$O) ($P > 0{\cdot}1$). A significant difference in median (i.q.r.) maximum anal squeeze pressure was shown between female controls with a previous obstetric history (140 (110–215) cmH$_2$O) and those who were nulliparous (180 (140–290) cmH$_2$O) ($P < 0{\cdot}05$). The combined results of the group were used for comparison with the patient group.

Episodes of transient IAS EMG inactivity caused by rectoanal inhibition were observed in the control group where there was a related preceding rise in rectal pressures with a resulting fall in anal pressures. Transient IAS EMG silence was also seen during micturition. In three individuals, increase in upper rectal pressure alone was associated with a fall in anal pressure. No other episodes of electrical silence seen in normal controls were not preceded by a rise in rectal pressure. These episodes of transient IAS inactivity lasted approximately two or three cycles of the IAS EMG sinusoidal activity and anal pressure was restored to resting levels within 10 s, i.e. the fall and subsequent recovery of anal pressure lagged behind the sphincter EMG events by several seconds.

The median (i.q.r.) frequency of daytime sampling episodes was 3 (1–7) per h in controls below the age of 55 years, 5 (2–7) per h in those over 55 years of age ($P > 0{\cdot}1$) and 4 (3–7) per h for the group as a whole; all controls had these episodes

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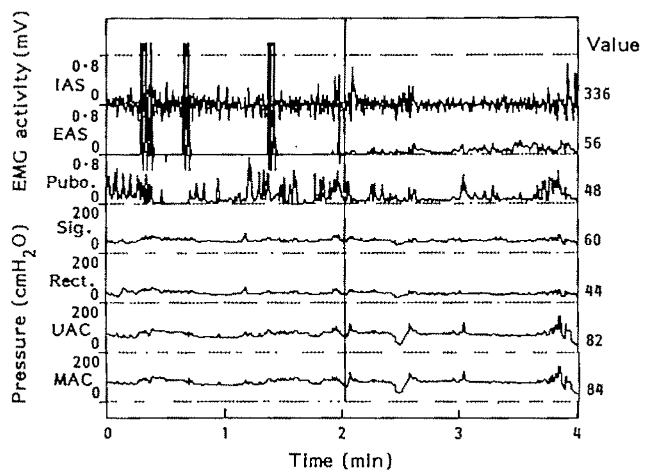

Figure 1 *Transient internal anal sphincter (IAS) relaxation in a control subject (marked by cursor). A rise in rectal pressure is followed by a transient decrease in IAS electromyogram (EMG) frequency and a fall in anal pressure; rectal pressure does not exceed anal pressure. EAS, external anal sphincter; Pubo., puborectalis muscle; Sig., rectosigmoid; Rect., mid-rectum; UAC, upper anal canal; MAC, mid-anal canal; Value, reading at position of cursor*

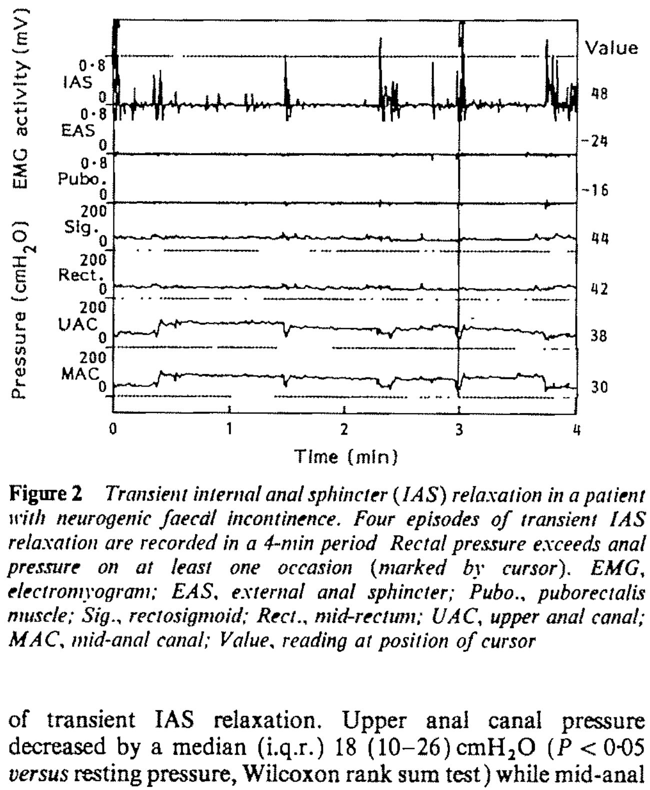

Figure 2 *Transient internal anal sphincter (IAS) relaxation in a patient with neurogenic faecal incontinence. Four episodes of transient IAS relaxation are recorded in a 4-min period Rectal pressure exceeds anal pressure on at least one occasion (marked by cursor). EMG, electromyogram; EAS, external anal sphincter; Pubo., puborectalis muscle; Sig., rectosigmoid; Rect., mid-rectum; UAC, upper anal canal; MAC, mid-anal canal; Value, reading at position of cursor*

of transient IAS relaxation. Upper anal canal pressure decreased by a median (i.q.r.) 18 (10–26) cmH$_2$O ($P < 0·05$ *versus* resting pressure, Wilcoxon rank sum test) while mid-anal canal pressure fell by 14 (8–19) cmH$_2$O ($P > 0·05$ *versus* resting pressure). Rectal pressure preceding transient IAS relaxation increased by a median (i.q.r.) 12 (9–17) cmH$_2$O ($P < 0·05$ *versus* resting pressure). Rectal pressure exceeded upper anal canal pressure in 22 subjects but was never greater than mid-anal canal pressure (*Figure 1*). EAS EMG recruitment (range 80–170 per cent) for the duration of IAS relaxation was seen in all controls.

Patients

The median (i.q.r.) IAS EMG frequency was 0·26 (0·21–0·32) Hz for patients with incontinence ($P < 0·01$ *versus* controls) (*Figure 2*); median ambulatory anal pressure was also significantly lower compared with controls (48 (34–68) *versus* 86 (72–102) cmH$_2$O, $P < 0·01$).

Transient IAS relaxation occurred more frequently in the patient group (median (i.q.r.) 9 (7–12) per h) than in controls ($P < 0·05$). These episodes lasted two or three cycles of IAS EMG activity and were associated with a preceding rise in rectal pressure (median (i.q.r.) 24 (12–35) cmH$_2$O; $P < 0·05$ *versus* controls) in all patients. Upper anal canal pressure decreased by a median (i.q.r.) 19 (11–24) cmH$_2$O, which was similar to controls ($P > 0·05$), while mid-anal canal pressure fell by a median (i.q.r.) 23 (14–28) cmH$_2$O, greater than the fall in controls ($P < 0·03$) (*Table 1*). Rectal pressure exceeded mid-anal canal pressure in 36 (75 per cent) of the patients during transient IAS relaxation (*Figure 2*). EAS recruitment was poor during these episodes (range 0–40 per cent).

Table 1 *Events during transient internal anal sphincter relaxation*

	Controls ($n = 44$)	Patients with incontinence ($n = 48$)
No. of daytime relaxations per h	4 (3–7)	9 (7–12)*
Decrease in upper anal canal pressure (cmH$_2$O)	18 (10–26)	19 (11–24)
Decrease in mid-anal canal pressure (cmH$_2$O)	14 (8–19)	23 (14–28)*
Increase in rectal pressure (cmH$_2$O)	12 (9–17)	24 (12–35)*

Values are median (interquartile range). *$P < 0·05$ *versus* controls (Mann–Whitney *U* test)

Discussion

IAS electrical activity is continuous during normal ambulation; electrical silence normally occurs only during anorectal sampling, passage of flatus, defaecation, micturition and sleep. This low-frequency sinusoidal EMG activity recorded from the IAS has been demonstrated to be present regardless of electrode position in the sphincter muscle[3]. The traces obtained during the present study are comparable to those produced from the IAS by other workers from both animal studies and *in vitro* experiments using human material[3–5].

Transient IAS relaxation appears to be a normal physiological event allowing the sensitive epithelium of the upper anal canal to 'sample' rectal contents while maintaining continence[1,2,6]. These episodes, which are associated with a rise in rectal pressure and reduction in anal pressure, occur more frequently in patients with incontinence[1,3]. These episodes in combination with lack of support from a damaged EAS may contribute to faecal leakage[7]. Such physiological evidence of IAS dysfunction is supported by *in vitro* demonstration of abnormal adrenergic control in patients with idiopathic incontinence[8].

Transient IAS relaxation was observed in all controls and patients. This contrasts with the figure of 18 per cent for patients with incontinence reported by Sun *et al.* in a laboratory-based study[2]. A shorter median recording time of 35 min in the laboratory compared with 8 h for the present subjects may account for part of this difference. Given the median frequency of IAS relaxation of 4 per h, it might be expected that these phenomena would be observed in the laboratory in all patients during a 35-min recording. In the present study, as for Sun *et al.*[2], these episodes were not seen often in the laboratory and transient IAS relaxation frequently did not occur until 1 h after ambulatory recordings began. The various manipulations of the anorectum, which included EMG wire placement, manometer insertion and balloon distension, may interfere with the normal pathways and account for the absence of IAS relaxation during the first hour of assessment. The patient groups studied by Sun *et al.*[2] were also of different diagnostic categories whereas the present patients were highly selected with neurogenic incontinence that excluded rectal prolapse and associated disorders; this may account for the differences observed.

Alternatively, the catheter itself may contribute to these episodes of spontaneous relaxation because of an irritant effect that increases with time. This would not explain why the relaxations are more frequent or prolonged in patients with incontinence compared with controls[1,2]. Furthermore, prolonged recordings over a 24-h period by workers using a 5-cm diameter catheter, much larger than in the present study, indicate a variability in the frequency of such relaxations related to the fasting state and sleep, neither of which can be accounted for by catheter irritation alone[9].

The frequency of relaxation was significantly higher in patients with incontinence and the fall in mid-anal canal pressure during these episodes in such patients associated with poor EAS recruitment. It is recognized that these patients have denervation of the pelvic floor[10,11] with associated ultrastructural[12–14] and physiological[15–17] abnormalities of the EAS. This may account for the large fall in mid-anal canal pressure and poor EAS EMG recruitment in the present patients.

Enhanced rectal contractility and IAS relaxation has previously been reported in a subgroup of faecally incontinent patients[2,18]. A rise in rectal pressure was noted in 48 of the present patients associated with transient IAS relaxation, 36 of whom had rectal pressure exceeding anal pressure lasting 10–15 s on 7–12 occasions per h. These events will promote faecal leakage.

Laboratory assessment of transient IAS relaxation as a source of faecal incontinence appears inadequate because sampling events are rarely seen during the short-lived recordings. Although this paper has concentrated on the pathophysiology of IAS dysfunction, incontinence is a multifactorial disorder in which there are also abnormalities of rectal motility and somatic muscle function. It is believed that frequent and prolonged IAS relaxations put undue stress on the neurogenically damaged EAS and, therefore, exacerbate any tendency to faecal leakage.

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References

1. Miller R, Lewis GT, Bartolo DCC, Cervero F, Mortensen NJMcC. Sensory discrimination and dynamic activity in the anorectum: evidence using a new ambulatory technique. *Br J Surg* 1988; **75**: 1003–7.
2. Sun WM, Read N, Miner PB, Kerrigan DD, Donnelly TC. The role of transient internal sphincter relaxation in faecal incontinence. *Int J Colorectal Dis* 1990; **5**: 31–6.
3. Kerremans R. *Morphological and Physiological Aspects of Anal Continence and Defaecation.* Brussels: Editions Arscia, 1969.
4. Pennickx F. *Morphological and Physiological Aspects of Anal Function.* Leuven: Acco, 1981.
5. Monges H, Salducci J, Naudy B, Ranieri F, Gonella J, Bouvier M. The electrical activity of the internal anal sphincter: a comparative study in man and in cats. In: Christensen J, ed. *Gastrointestinal Motility.* New York: Raven Press, 1980: 495–501.
6. Kumar D, Waldron D, Williams NS, Browning C, Hutton MRE, Wingate DL. Prolonged anorectal manometry and external anal sphincter electromyography in ambulant human subjects. *Dig Dis Sci* 1990; **35**: 641–8.
7. Lubowski DZ, Nicholls RJ, Swash M, Jordan MJ. Neural control of internal anal sphincter function. *Br J Surg* 1987; **74**: 668–70.
8. Speakman CTM, Hoyle CHF, Kamm MA, Henry MM, Nicholls RJ, Burnstock G. Adrenergic control of the internal anal sphincter is abnormal in patients with idiopathic faecal incontinence. *Br J Surg* 1990; **77**: 1342–4.
9. Orkin BA, Hanson RB, Kelly KA, Phillips SF, Dent J. Human anal motility while fasting, after feeding, and during sleep. *Gastroenterology* 1991; **100**: 1016–23.
10. Womack NR, Morrison JFB, Williams NS. The role of pelvic floor denervation in the aetiology of idiopathic faecal incontinence. *Br J Surg* 1986; **73**: 404–7.
11. Bartolo DCC, Jarratt JA, Read MG, Donnelly TC, Read NW. The role of partial denervation of the puborectalis muscle in idiopathic faecal incontinence. *Br J Surg* 1983; **70**: 664–7.
12. Swash M. Histopathology of the pelvic floor muscles in pelvic floor disorders. In: Swash M, Henry MM, eds. *Coloproctology and the Pelvic Floor.* Oxford: Butterworth–Heinemann, 1992: 173–83.
13. Swash M, Gray A, Lubowski DZ, Nicholls RJ. Ultrastructural changes in internal anal sphincter in neurogenic faecal incontinence. *Gut* 1988; **29**: 1692–8.
14. Beersiek F, Parks AG, Swash M. Pathogenesis of anorectal incontinence: a histometric study of the anal canal musculature. *J Neurol Sci* 1979; **42**: 111–27.
15. Neill ME, Swash M. Increased motor unit fibre density in the external anal sphincter muscle in anorectal incontinence: a single fibre EMG study. *J Neurol Neurosurg Psychiatry* 1980; **43**: 343–7.
16. Neill ME, Parks AG, Swash M. Physiological studies of the pelvic floor in idiopathic faecal incontinence and rectal prolapse. *Br J Surg* 1981; **68**: 531–6.
17. Kiff ES, Swash M. Slowed conduction in the pudendal nerves in idiopathic (neurogenic) faecal incontinence. *Br J Surg* 1984; **71**: 614–16.
18. Read NW, Haynes WG, Bartolo DCC *et al.* Use of anorectal manometry during rectal infusion of saline to investigate sphincter function in incontinent patients. *Gastroenterology* 1983; **85**: 105–13.

Paper accepted 27 July 1992

Correspondence

An improved means of faecal diversion: the trephine stoma

Sir

The recent paper by Mr Anderson and colleagues (*Br J Surg* 1992; **79**: 1080–1) is clearly a step in the right direction to minimize an otherwise major surgical intervention. There is no doubt, however, that a great deal of skill and care is required to ensure that the correct loop of bowel is withdrawn. I am aware of one such operation where the sigmoid colon was transected and the distal loop brought to the surface by mistake, with catastrophic results.

In two patients I have used a laparoscopic technique to create a colostomy, both for palliation. The advantages are clear in that a thorough inspection of the abdominal contents is usually possible, the loop to be brought up is readily identified and can be dissected free, and the surgical insult to the patient is minimal. The initial pneumoperitoneum and laparoscopy is performed using the Hasson technique of open laparoscopy[1], particularly if there has been previous surgery or in the presence of obstruction. Before operation two stoma points are marked: one convenient for sigmoid colon and one for transverse colon. One or other of these sites is used to insert a second trocar. A third cannula is inserted in the right side of the abdomen at a convenient site, and this should be 12 mm to allow the passage of an Endo-GIA (Auto Suture, Ascot, UK) stapler. In both cases it was possible to mobilize the sigmoid colon, pass a vascular sling, and withdraw it up to the colostomy cannula. It is important to remember that in the insufflated (and therefore distended) abdomen the colon may not reach as easily to the surface, and one should make a trial of deflating the abdomen to ensure adequate but not excessive mobilization.

In the first patient, whose pelvis was obstructed by a massive carcinoma of the prostate, it was possible to extend the incision around the cannula and pull up the loop. An oxalbumin buffer (Biethium; Ethicon, Edinburgh, UK) was inserted as a bridge, which was sutured in place using 0 Vicryl (Ethicon), and then the colostomy was opened and sutured to the skin as usual using 2/0 catgut. This procedure created a definitive loop stoma without the need for glass rods or plastic bridges.

In the second patient, with irresectable rectal carcinoma, the Endo-GIA stapler was used to transect the distal sigmoid, requiring two passes of the instrument to ensure a good seal (the advent of the new 60-mm staplers will make this far easier). It was then possible to place further vascular staples across the mesentery to separate the bowel ends adequately. The proximal end was brought out as an end colostomy and sutured to the skin with catgut after widening the left iliac fossa port. No complications occurred with either patient, both of whom are alive 6 months later after radiotherapy and chemotherapy.

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1. Hasson HM. Modified instrument and method for laparoscopy. *Am J Obstet Gynecol* 1971; **110**: 886–7.

Anatomy and function of the anal longitudinal muscle

Sir

Further to the excellent and erudite Review by Messrs Lunniss and Phillips (*Br J Surg* 1992; **79**: 882–4) on the anal longitudinal muscle, I believe some justifiable confusion may exist in the literature over the distinction between the rectococcygeus[1] and anococcygeus[2] muscles. These muscle bundles, which are composed of smooth or non-striated muscle, are well developed accessory muscles of the anorectum in the rabbit. In that species the right and left anococcygeus muscles run from the anal longitudinal muscle to the upper coccygeal vertebrae. The single rectococcygeus bundle takes origin from the longitudinal muscle coat of the rectum and runs caudally between the anococcygeus bundles to the coccyx (*Figure 1*).

Surgical anatomists do not describe these muscles, yet the current edition of *Gray's Anatomy*[3] still refers to the 'two' bands of non-striated rectococcygeus, with a description that fits better with the anococcygeus.

Some years ago I examined this region during operation and studied specimens from abdominoperineal resection, but I was unable to convince myself of any equivalent to the accessory muscles of the rabbit anorectum. Clearly it would have been more appropriate to look at the anatomy in the intact cadaver pelvis, but time did not permit further study. However, I would speculate that, as the tail retracted and virtually disappeared during evolution (arrow in *Figure 1*), the rectococcygeus and anococcygeus might merge with surrounding tissues and eventually look like the structure illustrated by Courtney[4] and termed the 'iliorectococcygeus', which appears to be part of the levator ani complex and its fascia posterior to the rectum. Perhaps a study in comparative and developmental anatomy might throw more light on this issue?

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1. McKirdy HC. Functional relationship of the longitudinal and circular layers of the muscularis externa of the rabbit large intestine. *J Physiol* (*Lond*) 1972; **227**: 839–53.
2. Creed KE, Gillespie JS, McCaffery H. The rabbit anococcygeus muscle and its response to field stimulation and to some drugs. *J Physiol* (*Lond*) 1977; **273**: 121–35.
3. Williams PL, Warwick R, Dyson M, Bannister LH. *Gray's Anatomy*. 37th ed. Edinburgh: Churchill Livingstone, 1989: 1374.
4. Courtney H. Anatomy of the pelvic diaphragm and anorectal musculature as related to sphincter preservation in anorectal surgery. *Am J Surg* 1950; **79**: 155–73.

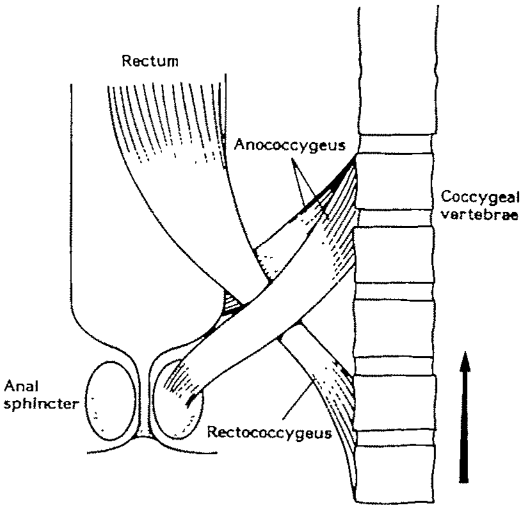

Figure 1 *Simplified representation of the rabbit rectococcygeus and anococcygeus muscles. The arrow represents retraction of the tail during evolution*

Limitations of laser treatment for malignant dysphagia

Sir

We read with interest the paper by Dr Shmueli and colleagues (*Br J Surg* 1992; 79: 778–80) on their experience with laser palliation of malignant dysphagia. Since 1989, we have treated 85 patients with 307 neodymium yttrium–aluminium–garnet laser treatments for malignant dysphagia. Almost all procedures were performed on an outpatient basis. There were no deaths associated with the treatment. No patient required insertion of an endoprosthesis; two suffered perforations, both of which were treated conservatively. Of the 85 patients, a further 38 received, in addition to the laser therapy, endoluminal radiation therapy plus external beam radiotherapy and chemotherapy. Patients who received both treatments required fewer ($P < 0{\cdot}001$) laser treatments than those who did not receive chemoradiation treatment. There were no treatment-related deaths.

Given these results, we are concerned at the 12 per cent complication rate, 4 per cent mortality rate, 21 per cent laser failure rate and 11 per cent intubation rate with its 9 per cent mortality rate reported by Shmueli *et al*. We feel that, from our experience, different conclusions regarding the value of laser (and particularly laser plus radiation) therapy in the management of malignant dysphagia can be made.

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Safety of fibreoptic endoscopy: analysis of cardiorespiratory events

Sir

We strongly support the conclusions of Mr Thompson and colleagues in their recent article on the safety of fibreoptic endoscopy (*Br J Surg* 1992; 79: 1046–9). Significant cardiorespiratory depression is particularly likely during colonoscopy, and monitoring by pulse oximetry is now mandatory. We wish to comment on the possible mechanisms suggested by the authors to explain the observed cardiorespiratory changes.

We recently studied alterations in arterial oxygen saturation and pulse rate in 80 patients undergoing colonoscopy[1]. Patients were separated into three groups according to the sedation: 16 received opiates and benzodiazepines as in the present study, 55 received only benzodiazepine, and nine received no sedation. In contrast to the results of Mr Thompson and colleagues, we found that the cardiorespiratory effects were highly dependent on the sedation used. Thirteen patients (81 per cent) sedated with opiate and benzodiazepine suffered significant oxygen desaturation (i.e. an oxygen saturation <90 per cent) in contrast to 17 patients (31 per cent) who received only benzodiazepine ($P < 0{\cdot}002$). None of the unsedated patients suffered significant desaturation ($P < 0{\cdot}001$); indeed, these patients developed no significant cardiorespiratory changes.

We concluded that the cardiorespiratory effects of colonoscopy are attributable wholly to the sedative regimen employed. Sedation should be kept to the minimum consistent with patient comfort and, whenever possible, opiates should be avoided.

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1. Paul AB, Brown R, Brewster N, Griffiths JMT. Sedation induced hypoxaemia in lower gastrointestinal endoscopy. *Endoscopy* 1992 (in press).

Laparoscopic *versus* open appendicectomy: a prospective evaluation

Sir

It was with great interest that we read the recent paper by Mr McAnena and colleagues (*Br J Surg* 1992; 79: 818–20). A preliminary report of these data had appeared in a letter[1]. We are concerned by the statistical analysis relating to wound infection as presented in *Table 1* in the *BJS* paper. Four of 36 patients receiving open appendicectomy developed wound infection as opposed to one of 27 treated by the laparoscopic route. Analysing these data by means of Fischer's (*sic*) exact test, we estimate a P value of 0·28, not $P < 0{\cdot}05$ as reported by the authors; we note that in the *Lancet* letter the data did not appear to be statistically significant.

We should also like to know whether there was a protocol for prophylactic antibiotic administration and surgical technique, or whether it was left to the surgeon's usual practice. If not, can the authors truly claim that laparoscopic appendicectomy significantly diminishes the risk of postoperative wound infection?

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1. McAnena OJ, Austin O, Hederman WP, Gorey TF, Fitzpatrick J, O'Connell PR. Laparoscopic *versus* open appendicectomy. *Lancet* 1991; 338: 693 (Letter).

Authors' reply

Sir

We thank Mr Sugrue and Ms Lee for their interest in this article. Perhaps we could draw attention to the sentence in our paper stating that 'all patients were given perioperative intravenous antibiotics in accordance with each consultant surgeon's usual practice'. Regarding the data on wound infection presented in *Table 1*, we have had the statistical analysis independently checked by a colleague at this hospital. A χ^2 test, which we believe to be appropriate given the numbers involved, gives $P < 0{\cdot}038$. Unfortunately the asterisk denoting significance was inadvertently omitted from the *Lancet* letter. Thus wound infection was indeed less frequent following laparoscopic than open appendicectomy in our study.

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Statistical comment

Mr Sugrue and Ms Lee are correct to question the use of the χ^2 test to compare wound infection rates of four of 36 (11 per cent) with one of 27 (4 per cent). The χ^2 test relies on an approximation that is valid only for large sample sizes, and in this example the problem is the small number of wound infections. For the χ^2 test to be valid in this context of comparing groups of a similar size, there would need to have been a total of at least ten wound infections observed in the study, rather than the five that were observed.

They are also correct in suggesting that Fisher's (not 'Fischer's') exact test is an appropriate one to use for this comparison, although I would have used a two-sided test (which gives $P = 0{\cdot}38$) rather than the one-sided test that they used to obtain $P = 0{\cdot}28$. However, it is worth bearing in mind that if the sample size is so small that one does need to use Fisher's exact test, then the data are likely to be rather uninformative. In this example there is a threefold difference in infection rates, and yet the difference is not statistically significant – a very 'soft' negative.

A final point that Mr Sugrue and Ms Lee did not pick up is that the χ^2 value used in the original paper was calculated wrongly, and rather than being 4·2 ($P = 0{\cdot}038$) should have been given as 1·16 ($P = 0{\cdot}28$). The underlying problem thus stems from an incorrect calculation rather than an inappropriate choice of statistical test.

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Place of routine operative cholangiography at cholecystectomy

Sir

We read with interest the recent article by Mr Corder and colleagues regarding selective cholangiography in patients undergoing cholecystectomy (*Br J Surg* 1992; **79**: 945–7). The debate has received new interest with the boom in laparoscopic cholecystectomy, doubtless because of the technical difficulties associated both with obtaining an operative cholangiogram and exploring the common bile duct (CBD) in the presence of an abnormal film[1].

We have recently reviewed a total of 743 open cholecystectomies performed over a 5-year period (1985–1990). Ninety-six patients (13 per cent) had undergone CBD exploration for proven stones. Based on the authors' preoperative selection criteria for cholangiography, we found that these criteria would identify only 44 per cent of our patients with duct stones. In addition, in our review the use of pre-exploratory operative cholangiography was not associated with any intrinsic complications.

Thus, in our cohort study of patients with CBD stones undergoing cholecystectomy, using the criteria of Mr Corder and colleagues, over half would have had their stones left *in situ*, with the potential for subsequent biliary leak and pancreatitis. We would further comment that routine preoperative intravenous cholangiography is a drain on both medical and administrative time and has considerable financial implications.

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1. Fligelstone LJ, Foster ME, Hay D. Laparoscopic cholangiography. *Ann R Coll Surg Engl* 1992; **74**: 252–3.

Authors' reply

Sir

We thank Mr Oshodi and colleagues for their comments. We are surprised that our suggested selection criteria for cholangiography would have identified only 44 per cent of the common bile duct (CBD) stones in their series. This finding is quite contrary to the data in other series reviewed in our paper. We would stress that *all* our criteria should be normal before cholangiography can be safely omitted. In addition, we would question whether ultrasonographic CBD diameter was measured in all the cases of Oshodi *et al.* Whether or not some CBD calculi are 'missed' by selective cholangiography, follow-up of series in which such a policy was used shows little evidence that such calculi cause future harm. In particular, the problems of 'biliary leaks and pancreatitis' are conspicuous by their absence. Mr Oshodi and colleagues also do not mention any falsely positive cholangiograms: their series would be unique if it contained none. Finally, nowhere in our paper do we advocate 'routine preoperative intravenous cholangiography'. Like others, we suggest that this procedure may help to screen selected patients before laparoscopic cholecystectomy.

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Laparoscopic operations in paediatric surgery

Sir

I read with interest Mr Miller's Leading Article on laparoscopic operations in children (*Br J Surg* 1992; **79**: 986–7). The problem of instrumentation is self-evident, but will doubtless be overcome in specialist neonatal and paediatric surgical centres. However, most pyloromyotomies are performed by general surgeons in district general hospitals without access to such equipment. As an enthusiastic laparoscopic surgeon I recently found myself about to start a pyloromyotomy in an infant, and I resented the idea of making an incision large enough to deliver the lesion into the wound. I made an incision much smaller than usual but found the lesion to be a large one, considerably larger than the size of my incision. It was technically straightforward to grasp the tumour gently inside the abdomen with a Babcock's forceps and split the muscle in the usual way under direct vision without enlarging the wound.

I would recommend this approach to any surgeon wishing to reduce the incision to one no larger than the 10-mm cannula used in adult laparoscopic surgery. In the interests of safety, this approach should of course be abandoned if there is the slightest doubt about the technical conduct of the muscle split.

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Potential candidates for small bowel transplantation

Sir

We read with interest the article by Ms Ingham Clark and colleagues (*Br J Surg* 1992; **79**: 676–9) regarding potential candidates for small bowel transplantation. While it is true that small bowel transplantation is an attractive alternative to permanent parenteral nutrition, we would disagree with the suggested length of residual small bowel necessary for a return to normal enteral nutrition.

We recently managed a 48-year-old woman who developed a superior mesenteric artery thrombosis with massive small bowel infarction while recovering from reconstructive vascular surgery for aortoiliac disease. She required resection of the whole of the small bowel distal to the fourth part of the duodenum plus a right hemicolectomy, with anastomosis of duodenum to the distal transverse colon. To perform this anastomosis the duodenum had to be mobilized off the ligament of Treitz to reach the transverse colon. It was not possible to fashion a cutaneous fistula because the remaining small bowel would not reach the skin. While recovering from this procedure the women received total parenteral nutrition. She was discharged 4 weeks after the second operation and, to our surprise, 1 year on, without any nutritional support, has remained remarkably well with preservation of body-weight and normal nutritional markers, except a lowered total iron-binding capacity. We would conclude that a nihilistic approach towards massive small bowel infarction is no longer appropriate and that it appears that, with only the duodenum remaining, normal lifestyle is possible in some patients.

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Book reviews

Surgical Management of Vascular Disease

P. R. F. Bell, C. W. Jamieson and C. V. Ruckley (eds). 280 × 220 mm. Pp. 1416. Illustrated. 1992. London: W. B. Saunders. £150.

This massive text of some 1400 pages represents the latest comprehensive tome on vascular disease. It is edited by three well known British vascular surgeons but contains contributions from several continents.

The first section of the book contains aspects of vascular disease in general and starts off with a history of arterial and venous surgery. Further chapters cover predisposing factors, diabetes and the natural history of atherosclerosis. There are further sections on investigation of atherosclerosis, arteritis and the autonomic nervous system, in addition to brief chapters on anaesthesia for vascular surgery and blood replacement therapy. Many of these chapters reflect personal views of the subject and are sometimes a little too brief to be definitive.

The difficulties of editing such a large book are manifest when there is inevitable overlap between different sections, but the scope and breadth of this text are very impressive. Some of the personal views expressed would not be universally accepted and might, in some cases, have little evidence to support them. I was also disappointed that there is little reference to the use of colour duplex scanning, which is now the most useful non-invasive tool in vascular diagnosis. Similarly, the use of transcranial Doppler ultrasonography during carotid endarterectomy is not included.

Chapters on such diverse subjects as vasculogenic impotence and congenital vascular anomalies are included, and there is a truly excellent section on venous disease. I was pleased to see a section on vascular surgical audit with guidelines for those who have little experience in this area. At the end of the book there is a brief section on experimental techniques in vascular surgery.

All in all, this is an excellent attempt at a comprehensive textbook of vascular disease that, for the most part, succeeds. Most of the authors are national or international authorities on their subject. The majority of the chapters are extremely well referenced and it is only a reflection on the speed of progress in the management of vascular disease that some of them already seem somewhat out of date. It is a great pleasure to see a British text of such high quality; it should become the standard reference book for vascular surgery.

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Atlas of Surgery of the Stomach, Duodenum, and Small Bowel

J. C. Thompson. 286 × 222 mm. Pp. 338. Illustrated. 1992. St Louis, Missouri: Mosby–Year Book. US $64·50.

This atlas of operative surgery reflects one surgeon's lifetime in upper gastrointestinal surgery and so represents a very personal approach. Throughout, it is beautifully illustrated with a great degree of clarity. However, in many cases the illustrations lack an appropriate degree of detail. For example, in the section on anatomy of the stomach, there is no description at all of the various tiers of lymph nodes used to describe resections for gastric cancer.

I am not at all sure whether the section on endoscopy adds anything: there is insufficient detail to be of use to anyone with but the very basics. Indeed, this is one of my major criticisms of the book as a whole: I am not at all sure at whom it is aimed. There is insufficient detail for any surgeon with a serious interest in upper gastrointestinal surgery, but a basic student is unlikely to read a book dedicated to just one area of surgery.

The balance of the text is also a little skewed for the 1990s. There are 20 pages describing resective procedures for benign gastroduodenal ulcer disease but just five on surgery for gastric cancer. The Japanese contribution to the latter is given just one line and there is no description or discussion of radical resection. In the section on duodenal trauma, there is no mention of iatrogenic endoscopic trauma, which (at least in this country) is as common as the non-iatrogenic variety. In the section on small bowel tumours there is no mention of carcinoids. Again, in the section on small bowel Crohn's disease there is nothing on stricturoplasty.

In summary, this is a well illustrated atlas of one surgeon's approach, but it is very personal. There is no time or space given to techniques other than those used by the author. For the higher surgical trainee with a special interest in gastroenterological surgery, there is insufficient detail to allow this to be used as a long-term reference work.

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Rob and Smith's Operative Surgery. Head and Neck. Parts 1 and 2. 4th ed.

I. A. McGregor and D. J. Howard (eds). 281 × 222 mm. Pp. 700. Illustrated. 1992. Oxford: Butterworth–Heinemann. £250.

The authors are to be congratulated on this new edition of *Operative Surgery*, which has long been overdue. The fourth edition is not so much a 'do it yourself' picture book, but is a well set out and reasoned approach to this demanding area of surgery. The emphasis on uniformity of presentation, using good-quality lined drawings and instructive text, adds to the authoritative feel of the two volumes. Ian McGregor and David Howard have brought together authors from the UK and North America with recognized expertise in the field of head and neck oncology. This is not solely a surgical text. Great emphasis has been placed on a team approach to the treatment of head and neck malignancy with close cooperation between radiotherapist, pathologist and reconstructive surgeon. The early chapters dealing with patient preparation and avoidance of complications serve to remind one of the potential morbidity of this type of surgery when practised by the inexperienced or occasional surgeon.

Volume 1 extensively covers aspects of facial reconstructive techniques, leading the reader through local skin flaps for facial lesions, regional myocutaneous flaps and finally free tissue transfer. The text and line drawings are clear to enable the surgeon to approach the problem of skin reconstruction in the head and neck in a rational way. Tumours involving the eyelids, nose, ear and lip are dealt with in specific chapters by the senior editor and inevitably reflect his personal experience. The treatment of oral cavity neoplasia receives a philosophical and practical approach in seven chapters and is commendable for its clarity. Volume 1 ends with short chapters on surgery for salivary gland tumours and neoplasia of the thyroid and parathyroid glands, as well as surgical access to the parapharyngeal space.

Volume 2 is devoted largely to the management of carcinoma of the laryngopharynx and covers pharyngolaryngectomy and reconstruction using a variety of techniques including myocutaneous flaps and free jejunal transfer, as well as colonic and gastric transposition. Laryngeal carcinoma is presented from a North American viewpoint with particular emphasis on near total and partial laryngectomy techniques, although total laryngectomy for endolaryngeal and pyriform sinus tumours is eloquently described. It is pleasing to see that functional reconstruction has not been forgotten, with chapters describing the current state of tracheo-oesophageal voice rehabilitation as well as thyroplasty techniques for laryngeal paralysis. Volume 2 concludes with the surgical treatment of tumours of the facial skeleton, including access techniques to the mid-face, as well as craniofacial techniques for tackling tumours of the middle and anterior cranial fossa. After reading these later chapters, it is clear that little is beyond the reach of the inventive head and neck surgeon.

This book is a must for any department with a serious interest in head and neck surgery. The authors have brought this subject into the 1990s with a textbook that embodies the principles of operative surgery.

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Modern Treatment of Severe Burns

Z.-Y. Fang, Z.-Y. Sheng, N. Li and S.-D. Ge (eds). 240 × 160 mm. Pp. 334. Illustrated. 1992. Heidelberg: Springer-Verlag. DM 298.

There can be little doubt that the greatest experience of severely burned patients is to be found in China. Thus this book should be welcomed by all; it is an excellent source of references (topographical errors aside) and reports of experimental work in model systems. The chapter on inhalation injury is interesting and thorough, as is that on 'Burns of special causes' (electrical, chemical etc.). There is a good review chapter on the methodology of culturing keratinocytes and their use, although the authors quote Western work rather than Chinese. There is extensive coverage of the problems associated with sepsis and shock. The chapter on the repair of wounds by grafting, especially the use of the 'Chinese' method of mixed autografting and allografting is interesting and informative. The thrust of the book is towards acute care, though in this regard the attention to pain control is poor, as are the discussions on reconstructive surgery, tissue expansion in particular. There is a disappointingly large number of typographical errors, especially mis-spellings in the references. Some of the formulae (for example on page 56) are also difficult to interpret.

This book represents a considerable achievement on the part of the authors in presenting, primarily for Western readers it is supposed, the body of Chinese experience in burn treatment. The main question is: How well does this translate and how relevant will Western clinicians find it to their own clinical practice? We suspect that most clinicians and other workers in the West will find this book an interesting curiosity, a particularly valuable source of information on the extensive Chinese research literature, but would not turn to it as an educational aid for the treatment of patients.

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Plastic and Reconstructive Surgery of the Breast

R. B. Noone (ed.). 284 × 220 mm. Pp. 533. Illustrated. 1991. USA: B. C. Decker.

This is a comprehensive description of breast conditions treated by plastic surgery. There are 41 chapters by 53 authors. In an introductory basic science section, anatomy is covered in a basic anatomical rather than a surgical anatomical way and, as such, is not particularly helpful. An exciting description of the embryology of the breast is followed by a disappointingly superficial chapter on physiology, but there is a useful chapter on silicones and breast surgery. Radiology gets excellent practical coverage but ultrasonography is not given the emphasis its increasing role demands.

The middle three sections cover developmental deformities, and augmentation and reduction mammoplasty. In the first, a chapter on gynaecomastia will be of interest to general surgeons and stresses that meticulous technique, preferably combining liposuction with excision, is necessary for a satisfactory cosmetic result. Augmentation and reduction mammoplasty, and correction of ptosis, are described in much detail with alternative techniques and complications well covered. Together with good coverage of psychosocial factors, the section on cosmetic procedures is perhaps the greatest strength of the book and will appeal particularly to plastic surgeons.

The last and largest section of 16 chapters deals with breast reconstruction. Every aspect is covered: reconstruction, implants and tissue expansion. With authors like John Bostwick and Carl Hartrampf, it is not surprising that this section is authoritative. However, the coverage is very much geared to the written word, with most of the illustrations being postoperative photographs rather than illustrations of details of technique. Perhaps this is appropriate to ensure that the techniques are learnt by apprenticeship, though experienced surgeons often pick up useful points from a textbook description of an individual technique. There are some disappointing sections – 'Nipple and areolar reconstruction' provides only one idiosyncratic technique and the results illustrated are far from ideal. The chapter on reconstruction after irradiation is also weak, with little consideration of the more difficult cases requiring chest-wall reconstruction that form a considerable part of the breast surgeon's workload. But these are small portions of a book in which the amount of background data and detail presented are generally very good.

Choice is difficult because of the explosion of books in this field. This book is a useful comprehensive account of techniques available, but it will not replace some of the more richly illustrated and visually explicit accounts of technical details, and it needs to be used in conjunction with these. If one looks at Hartrampf's own superb *Breast Reconstruction with Living Tissue*, one immediately sees the differing benefits of a text written by a technical master who can present his mastery with clarity and the present work, which gives a broader overview of the whole subject. The two types of book have complementary roles: perhaps Noone's book should be in every major library, but one such as Hartrampf's would be more necessary for personal everyday consultation (provided you agree with his approach and techniques).

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Atlas of Surgical Endoscopy

J. L. Parsky. 286 × 222 mm. Pp. 240. Illustrated. 1992. St Louis, Missouri: Mosby–Year Book.

Endoscopy is very much a skill required of gastroenterological surgeons, not only luminal endoscopy but also diagnostic and operative peritoneoscopy. This atlas is very much a manual of basic endoscopic techniques such as gastroscopy, oesophageal dilatation, laser therapy. and injection of varices. Similarly, colonoscopic and biliary procedures are discussed, as are simple laparoscopic procedures such as cholecystectomy and appendicectomy. The format is a brief description on one page, with a line diagram or artist's monochrome drawing on the opposite page. The text is pithy and didactic while the drawings are straightforward. This is quite a large book for such a small public and I had an uncomfortable feeling about the number of trees used to produce this modest tome. I felt that the text and diagrams were too simplistic to help a beginner in this essentially manual skill, and yet they were insufficient to be useful in making a diagnosis and treating the more unusual. As for laparoscopic techniques, the scope is widening so rapidly and the field changing so much that the section is already obsolete. The book was quite fun to browse through but not, I fear, one to buy.

M. G. W. Kettlewell

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MCQs in Applied Basic Sciences

K. M. Mokbel. 213 × 137 mm. Pp. 121. Illustrated. 1992. Dordrecht: Kluwer Academic. £7·50.

This small paperback should fit neatly into the pocket of the surgical trainee preparing for his or her revised Fellowship examination. It purports to be a whetstone on which the Fellowship candidate can sharpen surgical knowledge. I am sure that the surgeon in training so using this book will find it a worthwhile addition to an already extensive reading list. In just over 100 pages this well laid out text contains a total of 299 five-part multiple choice questions on eight different subjects, ranging from 100 questions on anatomy to nine on clinical immunology. However, if the candidate expects a list of actual Fellowship questions (with answers) that have previously come up and may come up again he or she will be disappointed. Nevertheless, used in the way the author intended, this book seems well worth its modest price.

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Jones' Clinical Paediatric Surgery – Diagnosis and Management. 4th ed.

J. M. Hutson, S. W. Beasley and A. A. Woodward (eds). 232 × 208 mm. Pp. 302. Illustrated. 1992. Carlton, Victoria: Blackwell Scientific. £29·50.

This is the fourth edition of this popular textbook on paediatric surgery formerly edited by Peter Jones but now with three new editors. All the chapters are by the staff of the Royal Children's Hospital, Melbourne, Australia. There are chapters on neonatal emergencies, head and neck, the abdomen, urinary tract, trauma, orthopaedics, chest, and skin and soft tissues. The purpose of the book is to provide a comprehensive guide on paediatrics and paediatric surgery for senior medical students, resident staff and general practitioners. It succeeds in this aim.

There are important and excellent chapters on antenatal diagnosis and genetic counselling and the care and transport of the newborn. There is comprehensive coverage of subjects including orthopaedics, ear, nose and throat and eyes, but cardiac surgery is omitted. I have very few criticisms; in the chapter on spina bifida the highest incidence of defects was stated to be lumbosacral, which contrasts with experience in this country where thoracolumbar defects are seen more frequently. Similarly, in the first-aid treatment of gastroschisis more emphasis should have been placed on the position of the child and eviscerated abdominal contents to prevent strangulation. The illustrations and line diagrams are clear and relevant. Details of surgical treatment are kept to a minimum with very little discussion on the various options. This is probably correct in a textbook aimed at medical students.

I personally preferred the format of the previous editions, which measured 9 × 6" rather than the new size of 9 × 8". The price of the volume is right and it should be available in every paediatric and paediatric surgical unit as recommended reading for medical students and house officers. Higher surgical trainees should purchase the book as an example of an excellent framework for developing skills in their chosen specialty.

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Textbook of Surgery – Pocket Companion

D. C. Sabiston and H. Kim Lyerly. 210 × 102 mm. Pp. 1044. Not illustrated. 1992. Philadelphia, Pennsylvania: W. B. Saunders. US $18·95.

This compact text is intended to serve as a portable introduction to the 14th edition of David Sabiston's *Textbook of Surgery: The Biological Basis of Modern Surgical Practice*, each chapter of the *Companion* being a concise version of its counterpart in the larger tome. The book is certainly shaped to fit a white coat pocket, but has almost 1000 pages of closely packed small print. Its contents are wide ranging and up to date with sections on laparoscopic surgery and surgical aspects of acquired immune deficiency syndrome, but I found it curiously erratic in the emphasis given to different surgical specialties. Paediatric surgery is given only 12 pages, confined to a discussion of the more common neonatal problems. The 16 pages on urology do not contain a classification of testicular tumours or guidance on the management of acute urinary retention. Vascular and cardiothoracic surgery, on the other hand, fill over one-quarter of the book. Their 260 pages contain detailed formulae for the calculation of left ventricular volume and a table of data on 'oxygen consumption during profoundly hypothermic, non-pulsatile, hemodiluted cardio-pulmonary bypass in monkeys'.

This is a well indexed book and I particularly enjoyed the short introductory chapter on the development of surgery. However, it weighs 0·5 kg and, rather than lug it around in my white coat pocket, I think I would pop back to my office or the hospital library and consult the complete work. My registrar agrees.

A. Mitchell

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ABC of Vascular Diseases

J. H. N. Wolfe (ed.). 295 × 210 mm. Pp. 79. Illustrated. 1992. London: British Medical Journal. £12·95.

This book is a compilation of articles edited by John Wolfe and published in the *British Medical Journal*. The key features of the series lie in the clarity and simplicity of presentation and, particularly, in the illustrations. The book is a very easy and interesting read. It covers the medical aspects of vascular surgery, together with some of its associated surgical techniques such as angioplasty, but is not a textbook of operative vascular surgery. Though not fully comprehensive (upper-limb reconstructive surgery and treatment of renal and mesenteric ischaemia are not covered), it does have sections on convalescent problems, rehabilitation of the amputee and arteriovenous malformations. The content, which is fully up to date with sections on thrombolysis in the acutely ischaemic limb and use of vein collars in femorodistal bypass, sticks to accepted and non-controversial views; while plenty of statistics are included there are no references. This book will be of interest to surgeons in training and to those not in the field who need an update on what vascular surgery has to offer. Its greatest appeal, however, will be to the undergraduate, for whom it will provide a fairly comprehensive text rather along the lines of a much expanded set of lecture notes. I thoroughly recommend it.

S. Parvin

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Notices and announcements

19–20 March 1993
2nd European Congress on Ambulatory Surgery
Brussels, Belgium
Information: Dr Cl. De Lathouwer, Brussels One Day Clinic, Nouvelle Clinique de la Basilique, 37–47 Rue Pangaert, B-1080 Brussels, Belgium

29–30 March 1993
General Thoracic Surgery: Surgery of the Esophagus
Boston, Massachusetts, USA
Information: Department of Continuing Education, Harvard Medical School, PO Box 825, Boston, Massachusetts 02 117, USA

31 March–2 April 1993
UICC Kyoto International Symposium on Recent Advances in Management of Digestive Cancers
Kyoto, Japan
Information: Professor T. Takahashi, Department of Surgery, Kyoto Prefectural University of Medicine, Kamigyo-ku, Kyoto 602, Japan

5 April 1993
Injury Research Group 1993 Meeting
Milton Keynes, UK
Information: Dr R. N. Barton, North-western Injury Research Centre, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

14–16 April 1993
Association of Surgeons of Great Britain and Ireland Annual Meeting
Birmingham, UK
Information: Caroline Ross, Association of Surgeons of Great Britain and Ireland, at The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

18–22 April 1993
International Congress on Advances in Brain Revascularization
Eilat, Israel
Information: Orta Ltd, 2 Kaufman Street, PO Box 50 432, Tel-Aviv, Israel 61 500

19–22 May 1993
Eighty-fourth Annual Meeting of the American Association for Cancer Research
Orlando, Florida, USA
Information: AACR Office, Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, Pennsylvania, USA

3–5 June 1993
First European Congress of the European Association for Endoscopic Surgery
Cologne, Germany
Information: Medikon-Heide Harzheim, Irmtraud Surmann, PO Box 50 14 70, D-5000 Köln, Germany

7–8 June 1993
8th International Symposium – Applied Physiology in Clinical Respiratory Care
Rotterdam, The Netherlands
Information: Dr O. Prakash, Thorax Centre BD 164, Dijkzigt Hospital, Dr. Molewaterplein 40, 3015 Rotterdam, The Netherlands

8–11 June 1993
World Association of HPB Surgery 1st European Congress of Surgery
Paris, France
Information: EHPBS Congress Secretariat, Congress House, 65 West Drive, Cheam, Surrey SM2 7NB, UK

9–12 June 1993
The Endocrine Society 75th Annual Meeting
Las Vegas, Nevada, USA
Information: Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

4–9 July 1993
Endosurgery – the State of the Art
Hamilton Island, North Queensland, Australia
Information: Kathy Noble, Centre for the Study of Endosurgery, Department of Surgery, Alfred Hospital, Commercial Road, Prahran, Victoria 3181, Australia

5–8 July 1993
First International and Eighth European Conference on Clinical Hemorheology
Vienna, Austria
Information: Professor E. Ernst, Department of Physical and Medical Rehabilitation, University of Vienna, AKH Währinger Gürtel 18–20, 1097 Vienna, Austria

6 July 1993
Current Issues in Epidemiology: the Prevention and Control of Chronic Disease
Cambridge, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

6–17 July 1993
Current Practice in Neonatal and Paediatric Surgery
Manchester, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

8–9 July 1993
Surgical Research Society Meeting
Dundee, UK
Information: Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

8–10 July 1993
XVIIIth International Update on Liver Disease
London, UK
Information: Professor N. McIntyre, University Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

8–10 July 1993
5th South-east European Symposium of Paediatric Surgery
Graz, Austria
Information: Professor M. E. Höllwarth, Department of Paediatric Surgery, University of Graz, Heinrichstraße 31, A-8010 Graz, Austria

6–8 August 1993
First Asian Pacific Congress of Endoscopic Surgery
Singapore
Information: Maggie Phang, Congress Secretariat, Conference and Exhibition Management Services, 09-43 World Trade Centre, Singapore 0409

22–27 August 1993
International Surgical Week – 35th World Congress of the International Society of Surgery
Hong Kong
Information: Congress Secretariat, ISW Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

27–29 August and
30 August–2 September 1993
Second International Conference of Gastroenterology
Hong Kong and Chengdu, China
Information: Conference Secretariat, Room 1611-13, World Finance Centre, North Tower, Harbour City, Kowloon, Hong Kong

1–3 September 1993
4th International Congress – International Organization for Statistical Studies on Diseases of the Oesophagus
Paris, France
Information: Michele Liegeon, 2 Boulevard de Montparnasse, 75 015 Paris, France

7–10 September 1993
6th International Congress on Interventional Ultrasound
Copenhagen, Denmark
Information: Dr C. Nolsøe, Department of Ultrasound, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

15–18 September 1993
Eurosurgery '93
London, UK
Information: Professor J. P. S. Lumley, Secretariat, Eurosurgery '93, The Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, UK

SURGERY ABSTRACTS

Br. J. Surg. 1993, Vol. 80, February, 269–270

Summaries from the January issue of the American journal.

Isolation and long-term culture of human hepatocytes

Colleen M. Ryan, MD, Edward A. Carter, PhD, Roger L. Jenkins, MD, Laura M. Sterling, BS, Martin L. Yarmush, MD, PhD, Ronald A. Malt, MD, *and* **Ronald G. Tompkins, MD, ScD,** *Boston, Mass.*

Pressure-controlled perfusion of specimens of surgical hepatic resection produced improved yields of human hepatocytes for studies of long-term cultures. The effect of an extracellular matrix configuration on albumin secretion was evaluated by culture on a single layer of collagen or between double layers of collagen gel with Dulbecco's modified Eagle and Williams E media. Hepatocytes from 12 patients were maintained for more than 30 days, and in five of 12 experiments cells were cultured beyond 2 months. In the double gels the cells demonstrated typical polygonal liver cell morphology and higher albumin secretion ($p < 0.01$) up to 65 days; in contrast, in the single gels cells spread horizontally, and albumin secretion declined rapidly within 3 weeks. A comparison of media formulations showed that maximum albumin secretion occurred 5 days later but was maintained significantly longer with Dulbecco's medium ($p < 0.01$). The simple addition of a second layer of gelled collagen forming a collagen sandwich significantly stabilizes and supports the long-term culture of human hepatocytes. (Surgery 1993;113:48-54.)

Four-compartment fasciotomy and venous calf-pump function: Long-term results

Hans-Beat Ris, MD, Markus Furrer, MD, Stefan Stronsky, MD, Beat Walpoth, MD, *and* **Bernhard Nachbur, MD,** *Berne, Switzerland*

Twenty-one patients who underwent a four-compartment fasciotomy between January 1, 1986, and December 31, 1987, were revisited with respect to venous calf-pump function 32 to 56 months (mean, 46.2 months) after fasciotomy. Enrollment criteria consisted of an intact motor innervation, palpable pedal pulses, the absence of venous hypertension, and deep venous thrombosis before and during the treatment requiring fasciotomy and unimpaired ankle and knee joint function. None of the patients showed signs of chronic venous hypertension at assessment. Ambulatory strain-gauge plethysmography revealed no significant difference in recovery time and refilling volume values between the two limbs of each patient ($p > 0.1$) and between limbs in which fasciotomy was performed and those of normal subjects ($p > 0.1$). Color flow duplex scanning revealed patent popliteal veins with normal respiration-induced phasic flow pattern and absent reflux in all patients. All visible calf veins were patent, compressible, and without morphologic alterations. The fasciotomy wound was closed by delayed skin suture (the fascia remaining divided) in 48% and by skin grafts of the lateral incision in 52% of the patients, without significant difference in recovery time and refilling volume values ($p > 0.1$) at assessment. Fasciotomy does not lead to venous calf-pump dysfunction, irrespective of whether the wound is closed by delayed suture or skin grafts. (Surgery 1993;113:55-8.)

The effect of prednisone on pancreatic islet autografts in dogs

Yijun Zeng, MD, Camillo Ricordi, MD, Javier Lendoire, MD, Patricia B. Carroll, MD, Rodolfo Alejandro, MD, Debora R. Bereiter, BS, Andreas Tzakis, MD, *and* **Thomas E. Starzl, MD, PhD,** *Pittsburgh, Pa., and Miami, Fla.*

Prednisone was shown to induce hyperglycemia in dogs submitted to total pancreatectomy and pancreatic islet autotransplantation. The hyperglycemia caused by a 10-day course of prednisone, 1 mg/kg/day, starting on the day of operation was reversible within 1 week after steroid discontinuance. Three weeks after prednisone was stopped, there was no detectable adverse effect on glucose homeostasis as judged by fasting blood sugar levels and intravenous glucose tolerance test results. Four months after transplantation, glucose disappearance was delayed in animals previously treated with the prednisone compared with those previously treated with prednisone plus insulin or control animals. This was accompanied by lower insulin values on intravenous glucose tolerance testing and suggests a long-term subtle effect on islet function. The mechanism of the steroid effect is not known. However, this model could be used to test the diabetogenicity of other immunosuppressive agents including cyclosporine, FK 506, and azathioprine. (Surgery 1993;113:98-102.)

The effect of octreotide on hepatic regeneration in rats

Raj S. Pruthi, BA, BS, Marwan Farouk, FRCS, Wen-Hsin Tsai, MD, PhD, George Michalopoulos, MD, PhD, *and* **William C. Meyers, MD,** *Durham, N.C.*

The effect of the long-acting somatostatin analog octreotide on liver regeneration was studied in rats in vitro and in vivo. The effect of continuous subcutaneous octreotide infusion on regenerative liver weight and relative DNA synthesis was examined in rats that had undergone 70% hepatectomy. Administration of octreotide resulted in a 33% reduction of regenerating liver weight at 72 hours and a 67% reduction of regenerative hepatocellular hyperplasia at 24 hours. This effect was reversed within 12 hours after withdrawal of the drug. The mechanism for the inhibitory effect of octreotide appears to be indirect, because experiments in hepatocyte cultures did not demonstrate a direct inhibitory effect on serum-free or epidermal growth factor-induced regenerative hepatocyte prolifera-

*tion. Because insulin levels were suppressed by octreotide in the in vivo experiments, suppression of hepatotrophs may be the mechanism by which octreotide inhibits liver regeneration. (*SURGERY *1993;113:84-9.)*

Long-term results of entry closure and aneurysmal wall plication with axillofemoral bypass: A new procedure for repair of DeBakey type 3 dissecting aneurysm

Yasunaru Kawashima, MD, Ryota Shirakura, MD, Susumu Nakano, MD, Hikaru Matsuda, MD, Kazuhiro Taniguchi, MD, Mitsunori Kaneko, MD, Akira T. Kawaguchi, MD, Keiji Kadoba, MD, *and* **Ryosuke Matsuwaka, MD,** *Osaka, Japan*

*To prevent aneurysm rupture, avoid pseudoaneurysm formation, and preserve intercostal arteries, a new procedure for repair of DeBakey type 3 dissecting aneurysm was developed. Since January 1977, 28 patients have undergone repair of type 3 dissecting aneurysm. Fifteen patients with type 3b underwent this new procedure (group 1) and 13 patients with type 3a dissecting aneurysm underwent segmental graft replacement (group 2). In group 1 a permanent axillofemoral bypass was placed on the right side. Next the intrathoracic false lumen was opened longitudinally, the entry was closed, and the aneurysmal wall was sutured around the true lumen as tightly as possible. The operative mortality rate was 20% in group 1 and 31% in group 2. One of 15 patients in group 1 died of operation-related causes, whereas three patients in group 2 died. There were six late deaths: three in group 1 and three in group 2. Paraplegia occurred in neither group 1 nor group 2. The mean diameter of the plicated descending aorta was 24.0 ± 2.7 mm 3 months after surgery. No recurrence was detected in group 1. These results suggested that this new surgical technique for repair of type 3 dissection reduces the incidence of paraplegia and pseudoaneurysm formation. (*SURGERY *1993;113:59-64.)*

The mechanism of conversion of xanthine dehydrogenase to xanthine oxidase in acute pancreatitis in the canine isolated pancreas preparation

Isto H. Nordback, MD, *and* **John L. Cameron, MD, FACS,** *Baltimore, Md.*

*Four models of acute pancreatitis have been previously developed that use the ex vivo perfused isolated canine pancreas preparation. The four models include the intraarterial infusion of oleic acid (FFA) that mimics hyperlipemic pancreatitis, partial obstruction of the pancreatic duct with secretin stimulation (POSS) that mimics gallstone pancreatitis, a 2-hour period of ischemia before perfusion (ISCH 2) that mimics shock pancreatitis, and the infusion of cerulein at supramaximal stimulatory doses (CER), which lacks an obvious clinical counterpart. In the FFA, POSS, and ISCH 2 pancreatitis, but not in the CER pancreatitis, toxic oxygen metabolites, generated by the enzyme xanthine oxidase (XO), have been shown to be important mediators in the early pathogenesis. Ordinarily XO primarily occurs as xanthine dehydrogenase (XD) but can be converted to XO, which is the form that generates toxic oxygen metabolites. This conversion of XD to XO may take place either reversibly by way of sulfhydryl group oxidation or irreversibly by means of proteolytic cleavage of XD. This study was undertaken to investigate the mechanism of conversion of XD to XO in the FAA-, POSS-, and ISCH 2-induced pancreatitis models. CER pancreatitis was studied for comparison. After 4 hours of perfusion, pancreatitis was manifest by edema, weight gain, and hyperamylasemia in all four models. Dithiothreitol, a sulfhydryl group protector, ameliorated the weight gain in the FFA (40 ± 14 gm to 18 ± 13 gm; $p < 0.05$), POSS (28 ± 10 gm to 9 ± 3 gm; $p < 0.05$), and ISCH 2 pancreatitis (30 ± 13 gm to 15 ± 3 gm; $p < 0.05$), and ameliorated the hyperamylasemia in the POSS pancreatitis (12,062 ± 4304 units/dl to 5877 ± 2659 units/dl; $p < 0.05$). The CER pancreatitis was not ameliorated with dithiothreitol. A serine protease inhibitor of low molecular weight, phenylmethylsulfonyl fluoride, ameliorated only the CER pancreatitis (weight gain from 28 ± 10 gm to 17 ± 10 gm, $p < 0.05$; amylase activity from 38,116 ± 6491 units/dl to 23,372 ± 11,654 units/dl, $p < 0.05$), and not the FFA, POSS, or ISCH 2 pancreatitis. We conclude that in the three models of pancreatitis (FFA, POSS, and ISCH 2) that are mediated by toxic oxygen metabolites, XD is converted to XO reversibly by way of sulfhydryl group oxidation rather than irreversibly by way of proteolysis. In the CER pancreatitis, where XO does not play a role in the pathogenesis, proteolytic enzymes may be important mediators in the injury. (*SURGERY *1993;113:90-7.)*

Lovastatin and gallstone dissolution: A preliminary study

Kimberly D. Saunders, MD, Joe A. Cates, MD, Mohammad Z. Abedin, PhD, *and* **Joel J. Roslyn, MD,** *Sepulveda and Los Angeles, Calif.*

Background. *Lovastatin, an agent that reduces both serum and biliary cholesterol in humans, also inhibits cholesterol gallstone formation in an animal model. The present study was designed to assess the efficacy of lovastatin in gallstone dissolution.*

Methods. *All prairie dogs were fed a 1.2% cholesterol-enriched diet during the entire study. Gallbladders from five animals were examined at 3 weeks, and four of five gallbladders contained gallstones. Remaining animals were maintained on the 1.2% cholesterol-enriched diet and randomized to receive either water (n = 7); lovastatin, 8 mg (n = 7); ursodeoxycholic acid, 50 mg (UR, n = 7); or both drugs (lovastatin and UR, n = 7) twice daily by way of orogastric tube for 4 additional weeks. Response to therapy was determined by blinded examination of gallbladders.*

Results. *All three treatment groups had significant reductions in serum cholesterol, hepatic bile cholesterol, and hepatic cholesterol saturation index as compared to controls (water). Lovastatin induced a 28% response rate to dissolution therapy, which was equal to that achieved with UR, and the combination of lovastatin and UR produced a 56% response rate.*

Conclusions. *This preliminary study suggests that lovastatin, alone or in combination with UR, may be useful in dissolving gallstones in humans. (*SURGERY *1993;113: 28-35.)*

[illegible] authors

[illegible] *nal of Surgery* publishes original articles, [illegible] ading articles. Short notes, case reports and [illegible] orkshops are also accepted. All manuscripts are [illegible] mitted to editorial review.

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A covering letter must accompany all submissions and must be signed by all authors. The covering letter should state if an abstract of the work has been published and whether the authors wish the manuscript and/or illustrations to be returned if the work is not accepted. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents.

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Ethics

The Journal publishes all material relating to human investigation and animal experiments on the understanding that the design of the work has been approved by local ethical committees or that it conforms to standards currently applied in the country of origin. The Journal further reserves the right not to publish an article on the grounds that appropriate ethical or experimental standards have not been reached. Written consent must be obtained from the patient, legal guardian or executor for publication in *The British Journal of Surgery* of any details or photographs which might identify an individual. Evidence of such consent should be submitted with the manuscript.

Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 1988; **108**: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1·00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal considers that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

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The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 500 words, with no more than five references and one illustration.

Surgical workshops

These describe technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4 cm margins. Manuscripts which do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction,

methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name and address of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

Summary

The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biome[illegible] to abstracts from meetings is disc[illegible] unpublished communications is not ac[illegible] communications should be cited in the text, i[illegible] first author is responsible for confirming the[illegible] the material quoted with the originator.

In the text, references should be numbered consecutively by superscript: ^{1,2} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications.* New York: Springer-Verlag, 1981: 123–63.

Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991; **78**: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. The use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the *P* value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual *P* values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'.

Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, *P* values.

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

Coated VICRYL* (Polyglactin 910) Braided Synthetic Absorbable Suture, Sterile

PRESENTATION VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide in the ratio 90/10. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)_m(C_3H_4O_2)_n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided VICRYL suture material with a mixture composed of a copolymer of lactide and glycolide in the ratio of 65/35 and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Sutures may also be manufactured in the undyed form.

Coated VICRYL (Polyglactin 910) is available in non-needled lengths or attached to stainless steel needles of varying types and sizes, and is sterilised by ethylene oxide gas.

These sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action: Two important characteristics describe the *in vivo* behaviour of absorbable sutures. The first of these is tensile strength retention and the second absorption rate or loss of mass.

The general mechanism by which *in vivo* degradation of VICRYL (Polyglactin 910) occurs is hydrolysis.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at 14 days post-implantation approximately 65% of the original tensile strength remains. At 21 days approximately 40% of the original strength is retained for gauge sizes Metric 0.7 (6/0) and larger, and approximately 30% of the original strength is retained for gauge sizes Metric 0.5 (7/0) and smaller. All of the original tensile strength is lost between 28 and 35 days post implantation.

Intramuscular implantation studies in rats show that the absorption of these sutures occurs thereafter and is complete between the 56th and 70th day.

USES Coated VICRYL Synthetic Absorbable Sutures are intended for use where an absorbable suture or ligature is indicated.

DOSAGE AND ADMINISTRATION By implantation.

CONTRA-INDICATIONS, WARNINGS, ETC These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 7 days.

The safety and effectiveness of Coated VICRYL (Polyglactin 910) in neural tissue and in cardio-vascular tissue have not been established.

At the discretion of the surgeon, appropriate non-absorbable sutures may be used to provide additional wound support when Coated VICRYL (Polyglactin 910) Sutures are used in ophthalmic procedures.

Under certain circumstances, notably orthopaedic procedures, immobilisation by external support may be employed at the discretion of the surgeon.

Coated VICRYL (Polyglactin 910) Sutures, which are treated to enhance handling characteristics, require the standard surgical technique of flat and square ties with additional throws if indicated by surgical circumstances and the experience of the operator.

Acceptable surgical practice must be followed with respect to drainage and closure of infected wounds.

PHARMACEUTICAL PRECAUTIONS Recommended storage conditions: Below 25°C, away from moisture and direct heat. Shelf life is 5 years, the expiry date is shown on each pack. Do not re-sterilise the contents of the pack. Unused product from opened packs should be discarded. As with all sutures, care should be taken to avoid damage when handling. Avoid the crushing or crimping application of surgical instruments, such as needle holders and forceps to the strand, except when grasping the free end of the suture during an instrument tie.

LEGAL CATEGORY Not applicable.

PACKAGE QUANTITIES Coated VICRYL (Polyglactin 910) is available in various lengths in gauge sizes Metric 0.4 to 5.0 (8/0 to 2) and 3 metre lengths on LIGAPAK* reels Metric 2.0 to 4.0 (3/0 to 1). All products are sealed in aluminium foil packs and peel-apart overwrap pouches. The sales unit is a film-wrapped box containing 10, 12 or 24 packs.

FURTHER INFORMATION No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

PRODUCT LICENCE NUMBER 0508/0009.

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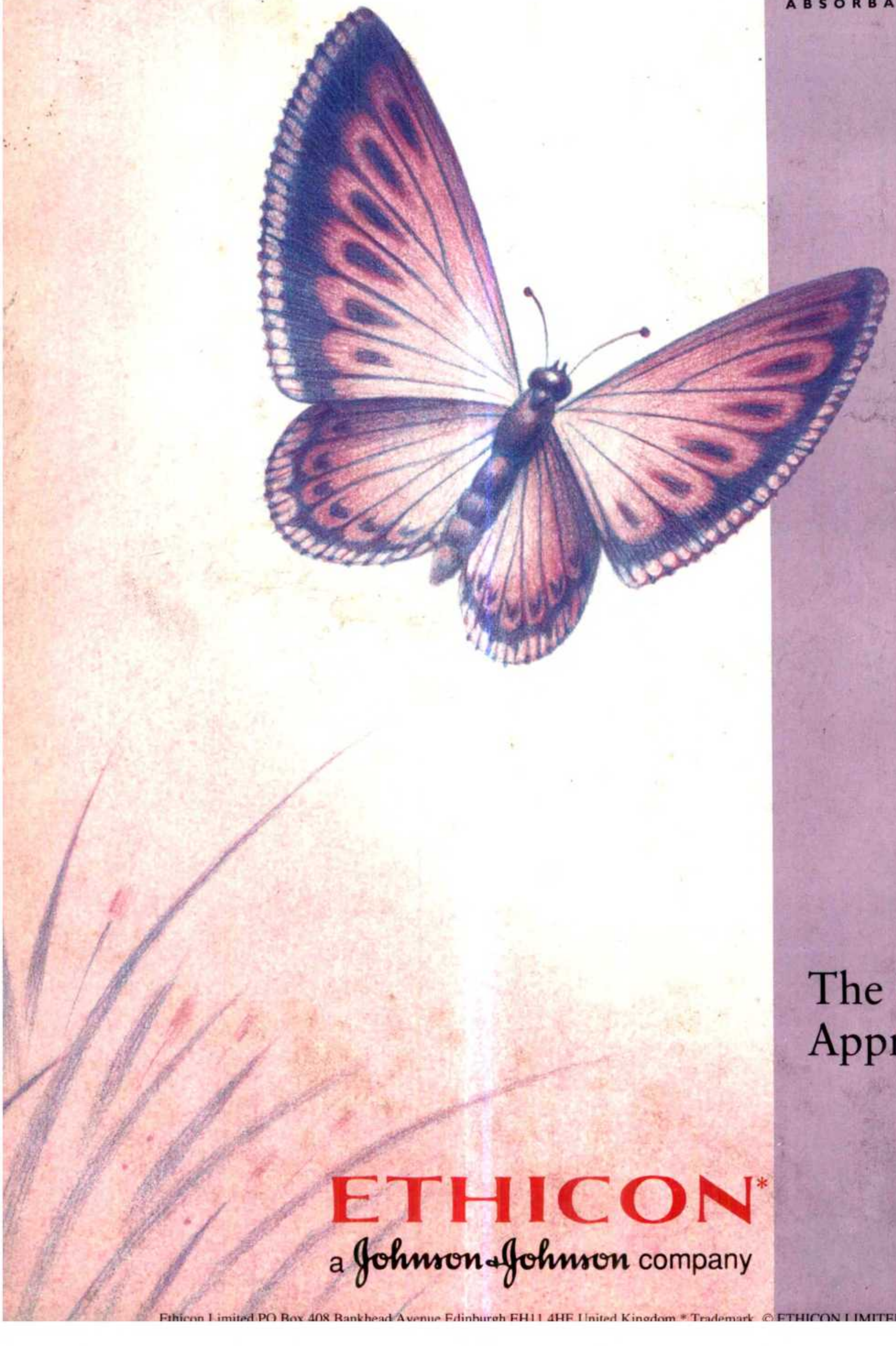

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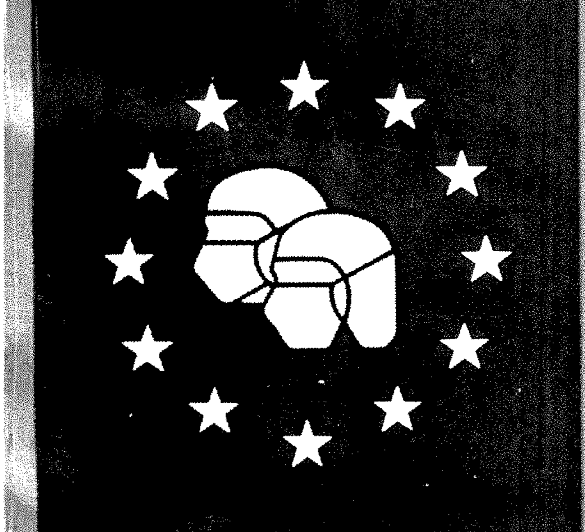

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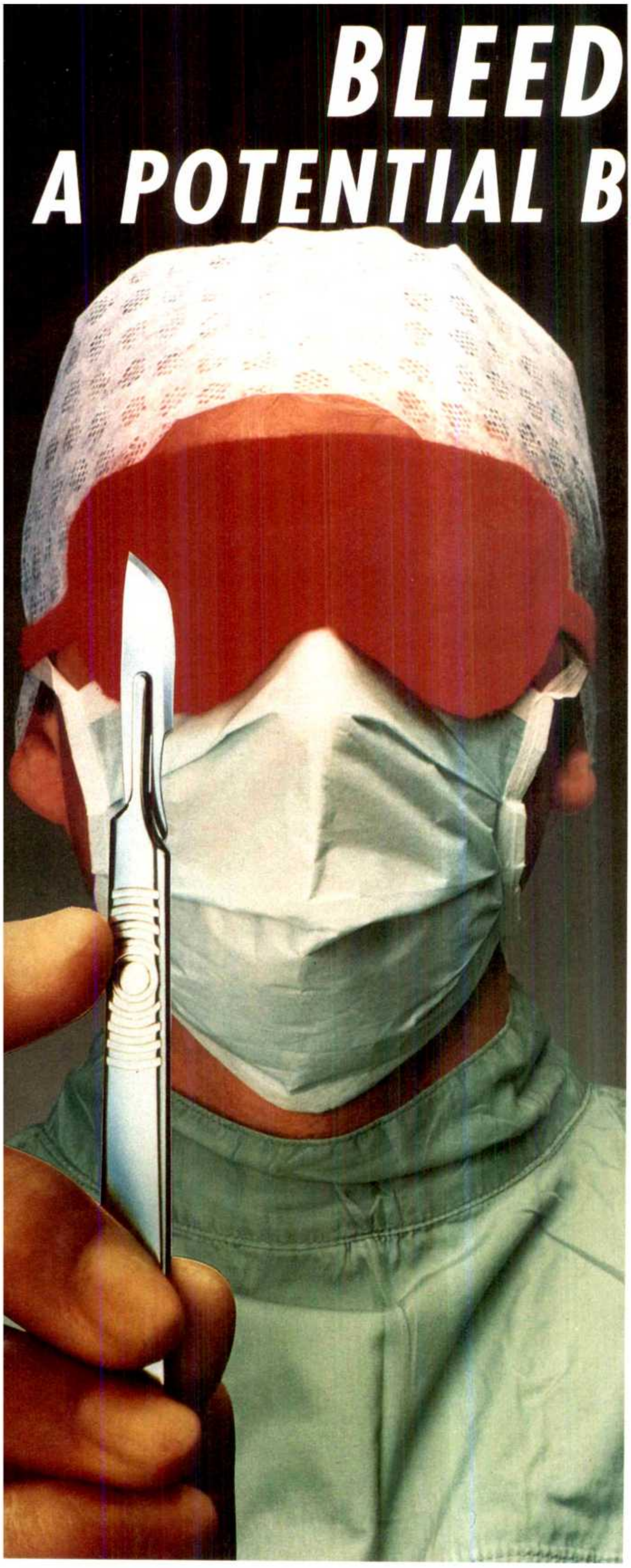

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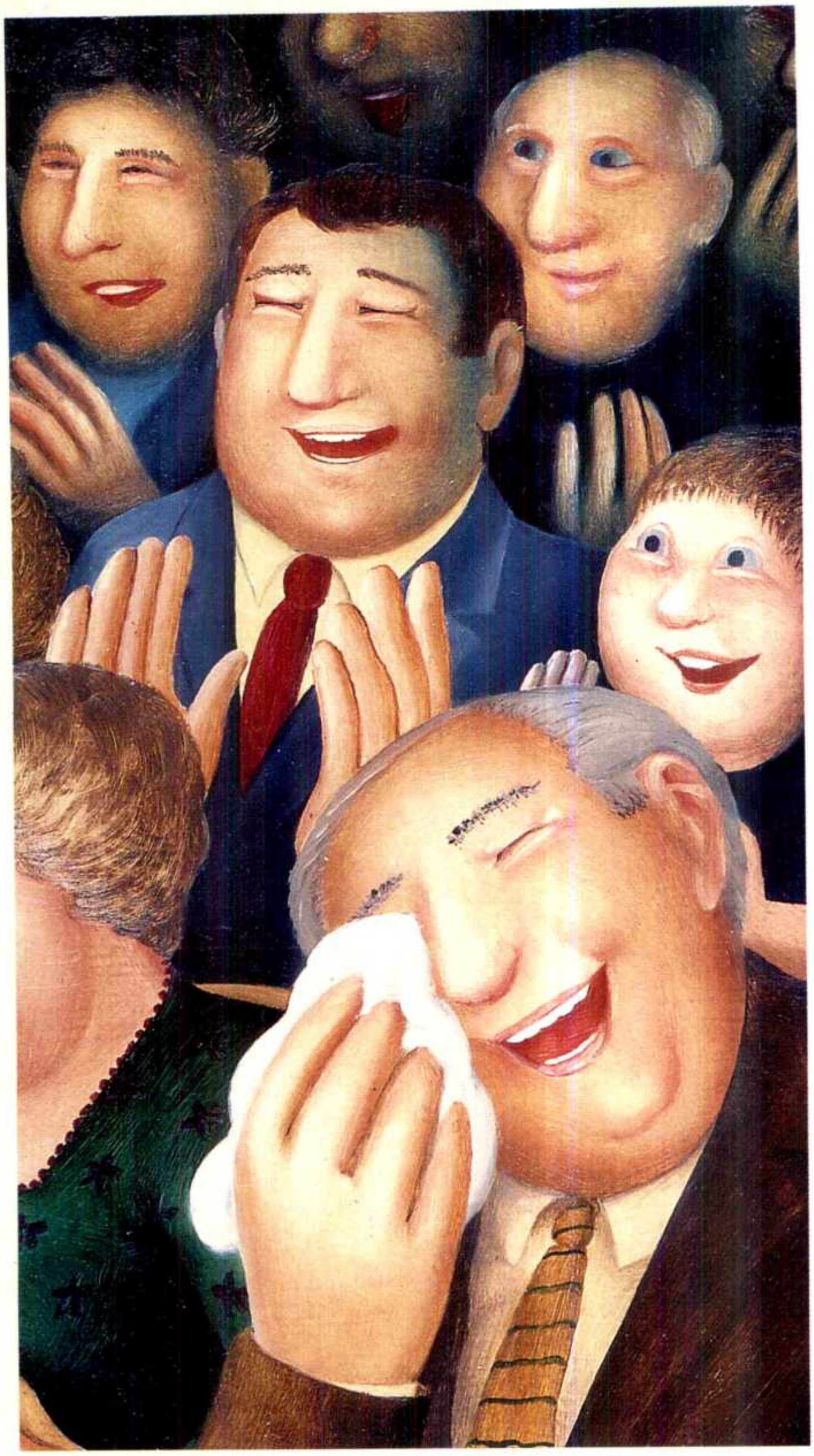

"They say laughter is the best medicine . . . when I was first told what I'd got I thought I'd never want to laugh again."

In a recent study[1] comparing the quality of life of prostate cancer patients receiving 'Zoladex' compared with those being treated with orchidectomy, it was found that men receiving 'Zoladex' gained a number of improvements in several important aspects of their lives.

Profile of Mood States (POMS) was used to assess such feelings as tension, depression, fatigue and vigour, while Functional Living Index: Cancer (FLIC) was used to measure physical ability, sociability, emotional state and family interaction.

The results of this study suggest that only the patient group treated with 'Zoladex' maintained a higher level of quality of life compared to their pre-treatment values.

Zoladex

goserelin

Treats the disease, enhances quality of life![1]

PRESCRIBING NOTES. Consult data sheet before prescribing. USE: Prostate cancer suitable for hormonal manipulation. **PRESENTATION:** A sterile depot containing goserelin 3.6mg. **DOSAGE AND ADMINISTRATION:** One depot injected subcutaneously into the anterior abdominal wall every 28 days. **CONTRAINDICATIONS:** Hypersensitivity to LHRH analogues. **PRECAUTIONS:** Patients at particular risk of developing ureteric obstruction or spinal cord compression. Consider initial use of an anti-androgen at the start of therapy. An increase in benign pituitary tumours has been observed in male rats following long-term repeated dosing. This finding is similar to that previously noted in this species following surgical castration (relevance to man not established). In mice, long-term repeated dosing with multiples of the human dose produced pancreatic islet cell hyperplasia and a benign proliferative condition of the pyloric region, also reported as a spontaneous lesion in this species (clinical relevance unknown). **SIDE EFFECTS:** Hot flushes, decrease in libido and occasional breast swelling and tenderness. Skin rashes (generally mild). Occasional mild bruising at injection site. Initial transient increase in serum testosterone may cause temporary increase in bone pain. Isolated cases of ureteric obstruction and spinal cord compression. **LEGAL CATEGORY:** POM. **PRODUCT LICENCE NUMBER:** (29/0198). **BASIC NHS COST:** £125.40 per depot. **'Zoladex' is a trademark.**

Further information is available from: ZENECA Pharma, King's Court, Water Lane, Wilmslow, Cheshire SK9 5AZ. ZENECA Pharma is part of the ICI Group.

Reference: 1. Cassileth BR, Soloway MS, Vogelzang NJ, *et al.* Quality of Life Research 1992; **1:** 323-330.

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BRAIDED SYNTHETIC
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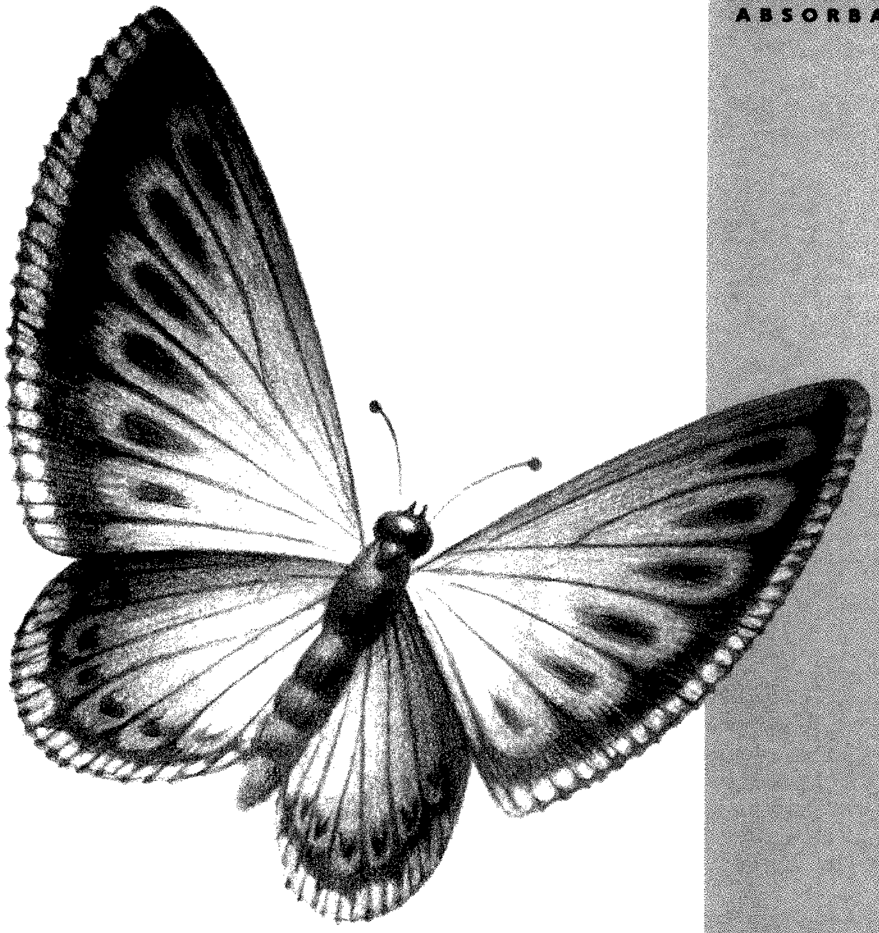

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Coated VICRYL* (Polyglactin 910) Braided Synthetic Absorbable Suture, Sterile

PRESENTATION VICRYL (Polyglactin 910) Suture is prepared from a copolymer of glycolide and lactide in the ratio 90/10. The substances are derived respectively from glycolic and lactic acids. The empirical formula of the copolymer is $(C_2H_2O_2)_m(C_3H_4O_2)_n$.

Coated VICRYL (Polyglactin 910) Sutures are obtained by coating the braided VICRYL suture material with a mixture composed of a copolymer of lactide and glycolide in the ratio of 65/35 and an equal amount of calcium stearate. This coating does not affect the biological properties of the suture.

VICRYL (Polyglactin 910) Sutures are coloured by adding D & C Violet No 2 during polymerisation of the lactide and glycolide. Sutures may also be manufactured in the undyed form.

Coated VICRYL (Polyglactin 910) is available in non-needled lengths or attached to stainless steel needles of varying types and sizes, and is sterilised by ethylene oxide gas.

These sutures are relatively inert, non-antigenic, non-pyrogenic and elicit only a mild tissue reaction during absorption.

Action: Two important characteristics describe the *in vivo* behaviour of absorbable sutures. The first of these is tensile strength retention and the second absorption rate or loss of mass.

The general mechanism by which *in vivo* degradation of VICRYL (Polyglactin 910) occurs is hydrolysis.

Subcutaneous tissue implantation studies of Coated VICRYL Suture in rats show at 14 days post-implantation approximately 65% of the original tensile strength remains. At 21 days approximately 40% of the original strength is retained for gauge sizes Metric 0.7 (6/0) and larger, and approximately 30% of the original strength is retained for gauge sizes Metric 0.5 (7/0) and smaller. All of the original tensile strength is lost between 28 and 35 days post implantation.

Intramuscular implantation studies in rats show that the absorption of these sutures occurs thereafter and is complete between the 56th and 70th day.

USES Coated VICRYL Synthetic Absorbable Sutures are intended for use where an absorbable suture or ligature is indicated.

DOSAGE AND ADMINISTRATION By implantation.

CONTRA-INDICATIONS, WARNINGS, ETC These sutures, being absorbable, should not be used where extended approximation of tissues under stress is required.

Sutures placed in skin and conjunctiva may cause localised irritation if left in place for longer than 7 days.

The safety and effectiveness of Coated VICRYL (Polyglactin 910) in neural tissue and in cardio-vascular tissue have not been established.

At the discretion of the surgeon, appropriate non-absorbable sutures may be used to provide additional wound support when Coated VICRYL (Polyglactin 910) Sutures are used in ophthalmic procedures.

Under certain circumstances, notably orthopaedic procedures, immobilisation by external support may be employed at the discretion of the surgeon.

Coated VICRYL (Polyglactin 910) Sutures, which are treated to enhance handling characteristics, require the standard surgical technique of flat and square ties with additional throws if indicated by surgical circumstances and the experience of the operator.

Acceptable surgical practice must be followed with respect to drainage and closure of infected wounds.

PHARMACEUTICAL PRECAUTIONS Recommended storage conditions: Below 25°C, away from moisture and direct heat. Shelf life is 5 years, the expiry date is shown on each pack. Do not re-sterilise the contents of the pack. Unused product from opened packs should be discarded. As with all sutures, care should be taken to avoid damage when handling. Avoid the crushing or crimping application of surgical instruments, such as needle holders and forceps to the strand, except when grasping the free end of the suture during an instrument tie.

LEGAL CATEGORY Not applicable.

PACKAGE QUANTITIES Coated VICRYL (Polyglactin 910) is available in various lengths in gauge sizes Metric 0.4 to 5.0 (8/0 to 2) and 3 metre lengths on LIGAPAK* reels Metric 2.0 to 4.0 (3/0 to 1). All products are sealed in aluminium foil packs and peel-apart overwrap pouches. The sales unit is a film-wrapped box containing 10, 12 or 24 packs.

FURTHER INFORMATION No suture related adverse reactions were reported during clinical trials, although a number of minor reactions were classified as being of unknown cause.

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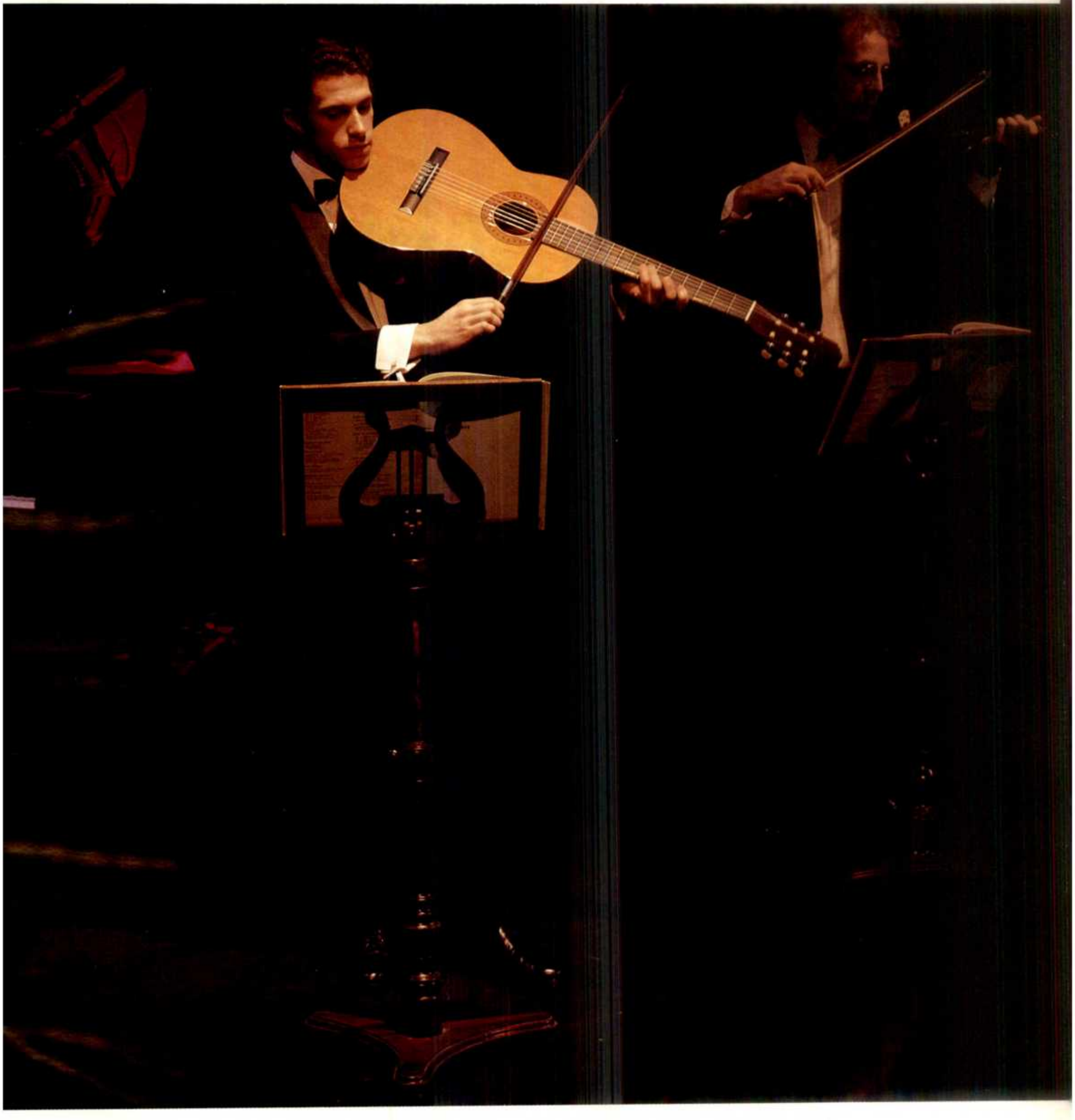

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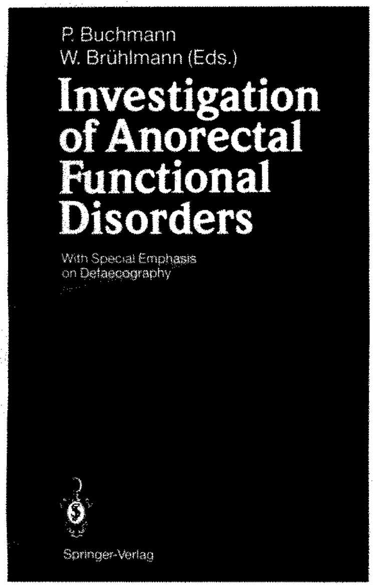

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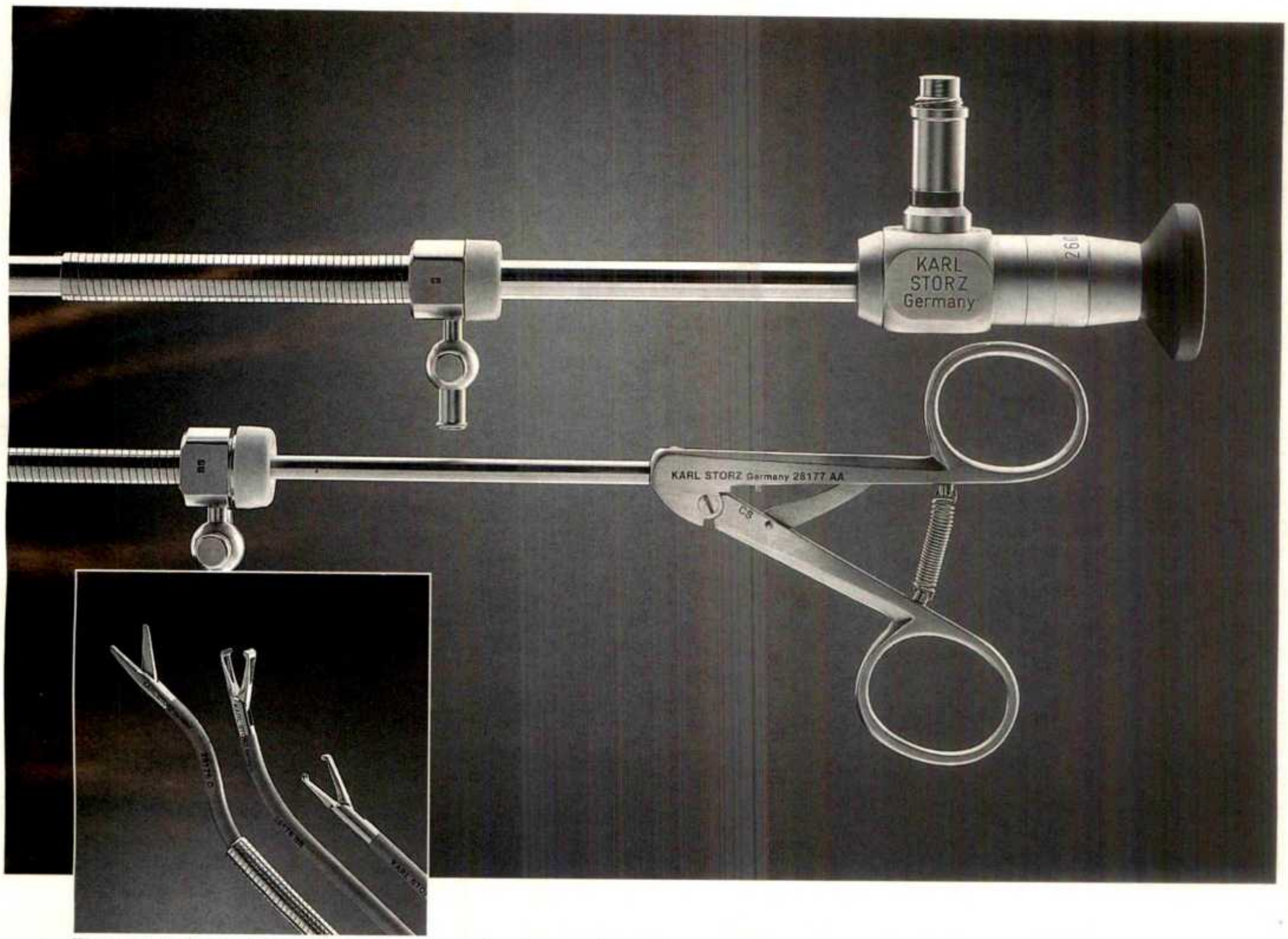

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References: 1. Bergqvist D. Post-operative thromboembolism. Frequency, etiology, prophylaxis. Berlin: Springer-Verlag, 1983. 2. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonar
embolism and venous thrombosis by perioperative administration of subcutaneous heparin. New Engl J Med 1988; 318:1162-1173. 3. Bergqvist D, Mätzsch T, Burmark U S et al. Low molecular weight heparir
given the evening before surgery compared with conventional low-dose heparin in prevention of thrombosis. Br J Surg 1988; 75:888-891. 4. Eriksson B I, Kälebo P, Anthmyr B O et al. Prevention of Deep-Vei
Thrombosis and Pulmonary Embolism After Total Hip Replacement. J Bone Joint Surg 1991;73A (4):484-493.

Further information is available from: **Kabi Pharmacia Cardiovascular, S-112 87 Stockholm, Sweden.**

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Br. J. Surg. 1993, Vol. 80,
March, 273

We present one new Member (elect) of the Council of the BJS Society (Mr Neil Mortensen) plus another two British Members of the Board (Messrs Crumplin and Phillips).

MR NEIL MORTENSEN

Neil James McCready Mortensen (born 1949) is a consultant surgeon at the John Radcliffe Hospital, Oxford. He graduated with honours in surgery from the University of Birmingham in 1973 and trained at Bristol, Exeter and St Mark's Hospital, London. Distinctions have included an Arris and Gale Lectureship at The Royal College of Surgeons of England (1978) and the Paul Hawley International Guest Scholarship of the American College of Surgeons (1980). He was appointed Consultant Senior Lecturer at Bristol in 1983 and moved to Oxford in 1986. He specializes in colorectal surgery with particular interests in anorectal physiology, rectal endosonography and inflammatory bowel disease; he has published widely in these fields. Mr Mortensen is Co-Editor of the *International Journal of Colorectal Disease*, Council Member of the British Society of Gastroenterology and past Treasurer of the Surgical Research Society.

MR MICHAEL CRUMPLIN

Michael Kenneth Hugh Crumplin (born 1942) was appointed a consultant surgeon at the Maelor Hospital, Wrexham, in 1977. He is a graduate of the Middlesex Hospital Medical School and trained in the south of England before becoming a senior registrar at the United Birmingham Hospitals. His research interests have included gastro-oesophageal reflux, biliary surgery and surgery of the elderly patient. He is currently the Chairman of the Court of Examiners of The Royal College of Surgeons of England.

MR ROBIN PHILLIPS

Robin Kenneth Stewart Phillips (born 1952) is a consultant surgeon at St Mark's Hospital and the Homerton Hospital, London; he was appointed to St Mark's in 1987. He has also been a senior lecturer in surgery at St Bartholomew's Hospital, London. Graduating from the Royal Free Hospital, his surgical training was based at St Mary's Hospital, London. He is a coloproctologist with special interests in Crohn's disease, anal fistula and colorectal carcinoma, including bile metabolism in familial adenomatous polyposis and anastomotic carcinogenesis.

Robin Williamson

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Br. J. Surg. 1993, Vol. 80, March, 274–276

Hepatectomy for liver metastases

The widest experience of hepatic surgery for metastatic spread of tumour has been gained with colorectal secondaries. For this particular condition the natural history of untreated disease is fairly well defined. Survival to 5 years from the time gross hepatic disease is discovered is so unlikely[1,2] that well-being with no detectable tumour after this period undoubtedly represents benefit from treatment. Some 20–30 per cent of patients undergoing potentially curative liver resection will achieve this goal[3,4], and a further 10 per cent will survive between 5 and 9 years, despite relapse with irresectable cancer, thereby indicating substantial palliation[1]. In one series only two of 19 patients who were free from disease after 5 years later developed a recurrent tumour; thus the majority of 5-year disease-free survivors may well be regarded as 'cured'[4].

These optimistic data should be considered from a more general perspective. About half of all patients with colorectal cancer present at some stage with hepatic metastases and around 5–10 per cent eventually become candidates for liver resection. Consequently, 1–3 per cent of all patients with colorectal cancer may benefit from hepatectomy. With such a common cancer this still represents a substantial number of people and the potential advantage for this minority justifies a rather aggressive screening policy for all patients who have undergone resection of a colorectal primary.

Individual judgement on the wisdom of resection for each patient is essential. Despite the large number of published series, establishing a valid set of selection criteria is difficult. Over the past 20 years hepatectomy for metastases has been characterized by a downgrading of some and removal of other contraindications. Originally all liver resection for metastases was considered questionable until, in 1980, Adson and van Heerden[5] produced a sound basis for the resection of solitary lesions. This type of assessment was expanded to include unilateral and then bilateral multiple lesions. At present, there is a broad consensus that liver resection is the treatment of choice for up to three colorectal metastases in the absence of extrahepatic disease, assuming that a satisfactory surgical margin can be achieved. Conversely, four or more individual nodules, extrahepatic disease and (to some extent dependent on surgical technique) a resection margin <10 mm are commonly regarded as contraindications[6].

The adoption of such strict criteria is arguably premature. It is true that, for patients with advanced liver metastases (with respect to number and/or distribution of lesions), tumours close to essential intrahepatic vascular structures, or disease involving other organs, surgery usually has only limited application for technical reasons. However, if a curative resection can be achieved despite such factors, survival follows a similar course to that found in patients who are commonly regarded as favourable candidates for resection[4]. A negative histological margin is, in fact, the paramount determinant of long-term success, as both eventual cure and prolonged survival despite cancer relapse are restricted to patients who have had complete tumour clearance[1]. The importance of a negative margin is so overwhelming that the greatest attention must be paid to the technical details of surgery and timing of resection[4].

To balance this absolute need for a negative margin with adequate liver function after resection demands an individualized surgical strategy. In this respect intraoperative ultrasonography, recognition of the hepatic vasculature and transformation of modern anatomical concepts into operative practice have been significant landmarks. Ultrasound-guided segment-orientated procedures are now available as well as standard hepatectomies[7]. They have widely replaced palpation-based wedge excision, which was associated with a high incidence of histologically positive margins[4]; this procedure should now be rare in modern hepatic surgery. Generally speaking, in non-cirrhotic patients with malignant liver disease, resections that allow a 1·5–2-cm margin may be recommended unless more than half of the hepatic parenchyma would need to be removed.

With respect to timing, surgical enthusiasm should be restrained until the biological behaviour of the metastatic tumour can be assessed. This 'test of time' is strongly recommended for small lesions, especially if there is more than one or if a major

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surgical procedure would be required. Cady and Stone[3] recommend a routine waiting period of 4–6 months, particularly for synchronous metastases. My policy is to restrict this interval to a maximum of 3 months, irrespective of the time of diagnosis relative to the primary procedure. However, a lesion of 5–6-cm diameter at first recognition is regarded as having already passed this test period and should be removed without further delay.

Despite sophisticated diagnostic and surgical technology, the majority of patients will eventually suffer tumour relapse. As the liver is the predominant site of recurrence, adjuvant chemotherapy with regional drug administration seems a logical supplement to complete surgical resection, at least for high-risk subgroups. However, the available data do not support the routine application of this technique[8]. Other approaches such as active specific immunization with virus-modified tumour cell vaccines[9] may show future promise, but all adjuvant treatment should be performed only in multi-institution prospective trials.

As an alternative, cryosurgery has been used over the past decade with some promise[10]. Although the patient most suitable for successful cryosurgery is also likely to be an excellent candidate for resection, there are certain indications for this new ultrasound-guided procedure. First is the small solitary lesion located deep within the right lobe that would otherwise require formal right hemihepatectomy with extensive loss of parenchyma. Second is bilateral disease in which complete resection would fail to preserve enough functional liver tissue. A combined approach with resection of the hemiliver predominantly involved and freezing of lesions in the remaining half may achieve the therapeutic goal at lower risk. Finally, cryosurgery may occasionally provide an option for limited recurrent disease when repeat hepatectomy cannot be justified for any reason.

Considering current facts and future perspectives, the following rule of thumb may be appropriate for colorectal secondaries in the liver. As no other therapeutic approach guarantees long-term tumour-free survival, or even an improved life expectancy, resection to benefit prognosis seems justified as long as complete tumour clearance can be achieved. This surgical aggression must be balanced by use of more sophisticated diagnostic tools, such that improved selection enlarges the group of patients treated successfully, while reducing the total number of operations performed. A better understanding of tumour biology is mandatory; this cannot simply be reflected in numbers, distribution or size of metastatic nodules. Finally, as the technical scope of surgery can hardly expand further, effective medical treatment, alternative to or at least adjuvant with surgery, is urgently needed.

Focusing finally on the wide spectrum of non-colorectal liver metastases, one may distinguish two different groups: non-endocrine and endocrine. In the former, very few patients present with disease confined to a resectable part of the liver and so the question of surgical treatment rarely occurs. If complete resection is possible, results for metastases from Wilms' tumour and, to some extent, for renal cancer are comparable to those for colorectal cancer[11]. Selection criteria and principles of surgical management are therefore similar. Long-term survival following hepatic resection has been reported anecdotally for gastric, adrenal and breast cancer, and for malignant melanoma, leiomyosarcoma of the small bowel and various other sarcomas. However, the likelihood of therapeutic benefit is so marginal that only true solitary lesions should be considered for surgery.

Patients with endocrine malignancy require a considerably modified strategy. Many of these tumours, such as carcinoid, islet cell carcinoma and gastrinoma, may grow extremely slowly. Even in the metastasized stage, the natural history can extend beyond 10 years. As hepatic secondaries of these tumours often cause severe symptoms, any effort at surgical resection appears worthwhile. This may support or enable effective medical treatment with the consequence of an unchanged survival time but a significantly improved quality of life. The options for surgical treatment of these patients include cytoreductive debulking, assuming that the tumour mass can be reduced by at least 90 per cent. On the other hand, a curative operation may be aimed for in highly selected patients with endocrine tumour metastases diffusely distributed but still confined to the liver. In such circumstances total hepatectomy (or cluster resection) followed by orthotopic liver transplantation may occasionally be the best treatment.

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1. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 1990; **77**: 1241–6.
2. Hughes KS, Simon RM, Songhorabodi S *et al.* Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. *Surgery* 1988; **103**: 278–88.
3. Cady B, Stone MD. The role of surgical resection of liver metastases in colorectal carcinoma. *Seminars in Clinical Oncology* 1991; **18**: 399–406.
4. Scheele J, Stangl R, Altendorf-Hofmann A, Gall FP. Indicators of prognosis after hepatic resection for colorectal secondaries. *Surgery* 1991; **110**: 13–29.
5. Adson MA, van Heerden JA. Major hepatic resection for metastatic colorectal cancer. *Ann Surg* 1980; **191**: 576–83.
6. Ekberg M, Tranberg KG, Andersson R *et al.* Determinants of survival in liver resection for colorectal secondaries. *Br J Surg* 1986; **73**: 727–31.
7. Bismuth H. Surgical anatomy and anatomical surgery of the liver. *World J Surg* 1982; **6**: 3–9.
8. O'Connell MJ, Adson MA, Schutt AJ *et al.* Clinical trial of adjuvant chemotherapy after surgical resection of colorectal cancer metastatic to the liver. *Mayo Clin Proc* 1985; **60**: 517–20.
9. Bohle W, Schlag L, Liebrich W *et al.* Postoperative active specific immunization in colorectal cancer patients with virus modified tumor cell vaccines: first clinical results with tumor cell vaccines modified with live but avirulent Newcastle Disease Virus. *Cancer* 1990; **66**: 1517–23.
10. Ravicumar TS, Kane R, Cady B *et al.* Hepatic cryosurgery with intraoperative ultrasound monitoring for metastatic colon carcinoma. *Arch Surg* 1987; **122**: 403–9.
11. Wolf RF, Goodnight JE, Krag DE, Schneider PD. Results of resection and proposed guidelines for patient selection in instances of noncolorectal hepatic metastases. *Surg Gynecol Obstet* 1991; **173**: 454–60.

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Perspectives in European surgery

Many readers of this Journal would feel themselves to be in some way professionally involved with Europe, perhaps because they are friendly with colleagues in other European Community (EC) countries or, at the very least, because they are apprehensive about the effect that decisions made in Brussels may have on their own practice. The interest in Europe is there; the problem is how to give it expression. The number of European surgical societies, associations and federations increases all the time. Some of these bodies designate themselves as 'Academies' or 'Colleges', which may give an impression of added status. Most have drawn up statutes and articles of association and appointed eminent people as honorary officers. Plans will have been made for an annual congress in some agreeable European centre and there may even be talk of a new journal. There is nothing wrong in this: it is agreed that closer communication between European colleagues is desirable and that British surgeons in particular have been guilty of isolationism. But equally it must be recognized that there are already too many meetings and certainly far too many journals. So what guidance should be given to the busy European surgeon who wishes to contact like-minded colleagues on both sides of the Channel but hesitates to participate in new societies whose worth he or she cannot evaluate?

Those bodies that have some official status within the EC and those that carry no such weight must be distinguished. The Community is essentially a law-making organization; its Commission sets the political agenda and proposes legislation to the Council and Parliament that affects all those within the Community. The importance of this arrangement is demonstrated in the current dispute over accreditation. The Commission receives advice from many quarters and has to be selective in its listening. Of the three bodies that represent hospital doctors and have a right of entry into the system, the Union Européenne de Médecins Spécialistes (UEMS) has the most direct impact on surgeons. Each specialty has its own Section that meets regularly and reports upwards in the EC mechanism. Member states each have two delegates to the Section; UK surgeons are represented through their Colleges and specialist associations. The monospecialist Sections received a recent boost to their influence by being entrusted with the establishment of European Boards that will supervise specialist training and certification. An important development is that the Permanent Working Group of Junior Hospital Doctors has won the right to be represented on the Boards.

This brief account of the statutory advisory bodies can do little more than acquaint surgeons with their existence and perhaps encourage them to learn more. The important point is that these are the routes into the decision-making process; the only way in which non-official professional associations, however prestigious, can influence events is to gain places on the Boards. This mechanism is specifically allowed for in the Board statutes.

Some years ago it occurred to French surgeons that, rather than create another association, it might be more effective to arrange a congress at which all existing national surgical societies could meet to discuss common problems, political as well as clinical. The annual meeting of the American College of Surgeons attracts some 10 000 delegates and is a major event in the world professional calendar. Europe has an equivalent population and a similar level of talent, so perhaps it should do likewise. The idea of Eurosurgery began in Strasbourg in 1988 and the first meeting was held in Paris in 1990, under the auspices of the Association Française de Chirurgie. Encouraged by its success, Eurosurgery took shape and the second meeting in Brussels in June 1992 was attended by 1600 delegates from 27 countries; the Secretary-General of the UEMS attended and sent a message of congratulations.

Eurosurgery is not another new society. It has no individual members but is a grouping of national associations that are free to join and leave as they please and whose common purpose is to share ideas on the practice and organization of surgery within Europe. Rather than being imposed from on high, Eurosurgery is a movement that originated in the younger generation of surgeons. Its shape is still not finalized: there is a small secretariat based in Paris and a committee of management on which all Community countries and a few others are represented, but with a chairman rather than president. The president of the congress changes each year and is nominated by the country whose turn it is to host the next meeting. Thus Paris 1990 had a Belgian president, Brussels 1992 had a British president, London 1993 will have a German president (because of Berlin 1994) and so forth.

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Although started by a group of general surgeons, Eurosurgery aims to include all disciplines and London will see the cooperation of all the British specialist associations with their European counterparts. The meeting is not confined to established consultants, and a major focus of discussion has been and will be training and harmonization, to which the Permanent Working Group of Junior Hospital Doctors has contributed so much. Nurses, physiotherapists and ancillaries are catered for in separate sessions and have full rights to attend every part of the programme. Free registration will be offered to all UK and Irish medical students. It was the secretary of the French association who suggested that the official language of the meeting should be English, a proposal that no Northern European could have made. Furthermore, at the instigation of the Mediterranean countries, this Journal has been chosen as the official vehicle for publication of the proceedings.

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Announcement

Eurochirurgie/Eurosurgery '93

Following the successful Second European Congress of Surgery in Brussels in June 1992, the Journal is pleased to continue its association with Eurochirurgie. Our plans include publication of the abstracts from Eurosurgery '93 as a supplement to the September issue of the Journal. All oral presentations and selected posters will be included in the abstract book of the meeting. This will be distributed free to all regular subscribers of the Journal.

Once again, the *BJS* invites submission of definitive manuscripts from papers presented at the meeting. These will be subjected to the normal review process of the Journal and those accepted will be published in a dedicated Eurosurgery issue.

Papers from the 1992 meeting appear in the current issue. The Editors encourage all contributors at Eurosurgery '93 to submit their contribution in an appropriate form to the *BJS*; detailed advice on preparation of manuscripts can be found in the Instructions to Authors at the back of each issue.

The Journal wishes every success to Eurochirurgie/Eurosurgery and the Editors join The Royal College of Surgeons of England and the numerous associated societies in welcoming European surgeons to London in September of this year.

C. D. Johnson
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Emergency laparoscopic surgery

The acute abdomen continues to demand a large proportion of the general surgeon's workload. Recent studies have demonstrated that management errors can be significantly reduced using selective laparoscopy and this should now become routine practice. The continuing advances in laparoscopic surgery that permit many emergency procedures to be performed by this route provide increased impetus for a combined approach using diagnostic and therapeutic laparoscopy for the management of the acute abdomen. Results of current studies must be awaited before the exact role of emergency laparoscopic surgery can be defined, but early reports suggest several advantages in using laparoscopy to manage conditions such as acute appendicitis, perforated peptic ulcer and gynaecological emergencies.

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Building on improvements in videocameras and instrument technology that have been central to the development of laparoscopic cholecystectomy[1], surgeons have become increasingly adventurous in the procedures that they perform laparoscopically. The rapid recovery and return to normal activity that follow laparoscopic surgery provide an extra incentive for the surgeon to adopt more laparoscopic techniques. Although the use of laparoscopy in emergencies is not new, it has become increasingly popular as operators have become more familiar with the techniques involved. It remains to be seen whether the problems of surgical expertise, training and theatre logistics can be solved to enable emergency laparoscopic procedures to become routine practice 'out of hours'. Of even more importance is to identify which operations are suitable for this form of treatment and for which conditions laparoscopic surgery provides advantages over the standard open operation. This review examines the current role of laparoscopy in the acute abdomen, both traumatic and non-traumatic, and attempts to rationalize its future contribution to this field of surgery.

Management of the acute abdomen

Evidence over the past two decades from studies using computer-aided diagnosis has demonstrated that surgical performance in the management of the acute abdomen is unsatisfactory[2]. Although computer-aided diagnosis can improve diagnostic accuracy by at least 20 per cent, it remains unpopular with many clinicians[3]. Other techniques that can also improve overall management of the acute abdomen include peritoneal lavage[4] and cytology[5], ultrasonography[6] and laparoscopy[7].

The hospital mortality rate for patients admitted with non-traumatic acute abdominal pain is 4 per cent, rising to 8 per cent in those undergoing surgery[8]. For conditions such as perforated peptic ulcer the figure rises to 23 per cent, related to the proportion of elderly patients and to delay in presentation or treatment[9]. For common conditions such as acute appendicitis, delay in treatment is also associated with increased perforation rates and provides a significant contribution to mortality and morbidity[10,11]. Efforts to reduce the incidence of management errors such as delays in operation[2] have inevitably been associated with an 'unnecessary' operation rate, no condition requiring surgery being found, for acute appendicitis that remains between 15 and 30 per cent[12]. It is difficult to evaluate formally the complications of an unnecessary laparotomy, but the incidence of morbidity following an unnecessary appendicectomy ranges between 13 and 17 per cent[13,14].

Diagnostic laparoscopy in the acute abdomen

One of the first major studies using laparoscopy as a diagnostic aid in the management of the acute abdomen was performed in North America[7]. It demonstrated that, in a group of 56 patients with acute abdominal pain, six of 27 who proceeded directly to laparotomy did not require an operation. However, laparoscopy performed before laparotomy in 29 patients revealed 18 who did not require laparotomy. Since then other studies have confirmed these results, concentrating mainly on lower abdominal and pelvic pain[15–20]. A study from London in which selective laparoscopy was performed in patients for whom the need for operation was uncertain reported a reduction in error rate from a potential figure before laparoscopy of 19 per cent to zero[21]. Furthermore, additional studies from the same centre demonstrated that the unnecessary appendicectomy rate in this 'uncertain' group after laparoscopy was only 8 per cent compared with 22 per cent in the group in which the clinician was certain as to the diagnosis[22]. Without laparoscopy the overall unnecessary appendicectomy rate in women would have been 39 per cent compared with 15 per cent in men. Other studies have confirmed these results[23,24] and endorse the opinion that all women with the diagnosis, after clinical assessment, of suspected appendicitis should undergo laparoscopy before appendicectomy[25].

Although most patients undergoing laparoscopy for acute abdominal pain will fall into a 'suspected appendicitis' group, laparoscopy can provide valuable information in many other conditions (*Table 1*) and, when performed across the whole spectrum of the acute abdomen, can become an important adjunct to the armamentarium of the emergency surgeon[27–29].

Table 1 *Diagnosis in 125 patients with acute abdominal pain undergoing laparoscopy in whom the clinical decision to operate was uncertain*[26]

Acute appendicitis	48
Pelvic inflammatory disease	24
Non-specific abdominal pain	23
Ovarian cysts	14
Peritoneal adhesions	4
Metastatic disease	3
Perforated diverticulitis	2
Ectopic gestation	2
Mesenteric infarction	1
Empyema of gallbladder	1
Torsion of appendix epiploica	1
Primary peritonitis	1
Retrograde menstruation	1

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This use of selective laparoscopy produces an overall final diagnosis of non-specific abdominal pain in 23 per cent of cases[26], which contrasts with figures in excess of 40 per cent from other studies[30]. In addition, the ability to make a diagnosis at laparoscopy allows the surgeon to discharge patients who are still symptomatic. The normal appendix can be visualized at laparoscopy in at least three-quarters of patients[31], a figure that with experience approaches 100 per cent[23,32]. Failure to visualize the appendix does not mandate removal as signs of right iliac fossa inflammation usually indicate the presence of acute appendicitis or, alternatively, another cause for the symptoms may be seen. The problem arises when the appendix cannot be seen or appears macroscopically normal with no other cause found to explain the symptoms[33]. Although it has been suggested that macroscopic assessment of the appendix is unreliable compared with final histological examination[34], it is debatable whether laparotomy should be performed when a normal appendix is seen at laparoscopy. In one series, no cause for the symptoms was seen in 23 of 125 patients undergoing laparoscopy[26] and in only four was appendicectomy performed: two because the appendix could not be seen, one because laparoscopy failed and one because the appendix looked inflamed although histological analysis later demonstrated only serosal inflammation. Not one of these four appendices showed mucosal inflammation and none of the remaining 19 patients in whom no further procedure was performed subsequently required appendicectomy.

Early recognition of gynaecological conditions such as pelvic inflammatory disease and the Fitz-Hugh–Curtis syndrome (perihepatitis associated with pelvic inflammatory disease)[35] permits early treatment, which is important if complications such as infertility are to be reduced[36]. More recently, laparoscopy has been used in the acute abdomen specifically to investigate suspected intestinal ischaemia after aortic reconstruction and may even be performed at the bedside[37].

Diagnostic laparoscopy for abdominal trauma

Over the past 30 years diagnostic peritoneal lavage has revolutionized the management of blunt abdominal trauma and become widely accepted as the first-line investigation[38]. However, although the sensitivity of peritoneal lavage remains >95 per cent[38], many patients undergo unnecessary laparotomy when no injuries requiring surgical treatment are detected. The mortality rate of a negative laparotomy for abdominal trauma, both blunt and penetrating, is 1·6 per cent and the morbidity rate around 20 per cent[39].

In his 1942 paper discussing the problems related to non-penetrating abdominal trauma, Estes mentioned the possible role of laparoscopy but concluded that it had not been in use long enough for adequate evaluation[40]. It was many more years before further evaluation of laparoscopy for abdominal trauma was undertaken[41]; subsequent reports from several centres have confirmed its value[28,29,42,43]. In a randomized controlled multicentre comparison of peritoneal lavage and minilaparoscopy under local anaesthesia[44], identification of patients with minor injuries not requiring laparotomy seemed easier by laparoscopy than peritoneal lavage. There was one unnecessary laparotomy in the 13 patients undergoing laparoscopy compared with three of 11 having peritoneal lavage; this difference is not statistically significant. In this study the sensitivity of both techniques was 100 per cent but laparoscopy had a specificity of 94 per cent compared with 83 per cent for lavage. Traumatic diaphragmatic hernia, often a difficult condition to diagnose, can be confirmed by laparoscopy[45]. In ten such cases suspected following computed tomography or contrast radiography (in addition to routine chest radiographs), laparoscopy revealed a ruptured diaphragm with herniation in six, a rupture without herniation in two and no abnormality in two, thus sparing these last patients an unnecessary laparotomy.

Acute abdominal conditions and therapeutic laparoscopy

The exact role of therapeutic laparoscopy for acute abdominal conditions remains poorly defined. With increasing experience in elective laparoscopic techniques, many surgeons are prepared to consider a similar approach for emergency conditions[46]. There are additional considerations associated with emergency therapeutic laparoscopy over and above those for elective procedures. The most important are surgical experience, training, and availability of equipment and operating time, particularly in hospitals with a busy emergency workload. Furthermore, the advantages of therapeutic, as opposed to diagnostic, laparoscopy remain to be demonstrated.

Acute appendicitis

Laparoscopic appendicectomy was first reported by Semm[47], who has been one of the pioneers of laparoscopic gynaecological surgery. The procedure is relatively straightforward and has recently been successfully performed by other surgeons[48–50]. Before videolaparoscopy became available many who performed diagnostic laparoscopy in cases of suspected acute appendicitis were undertaking laparoscopically assisted appendicectomy when an acutely inflamed appendix was seen[51]. A small incision could be made directly over the appendix which could then be grasped under laparoscopic guidance. Recent developments in videocameras have now rendered this technique redundant, perhaps prematurely[52]. Reports are now available of large series of laparoscopic appendicectomies in both adults and children, with excellent results[53,54]. In one[53], 678 patients underwent appendicectomy; a laparoscopic removal was attempted in 639 and was successful in all but 14. The operating time was only 15–20 min but the postoperative stay was surprisingly long, with many patients remaining in hospital for up to 7 days. Both acutely inflamed and perforated appendices were included and a retrocaecal position was not a contraindication. The surgeons in this series divided the appendix mesentery with bipolar electrocoagulation and applied a pretied ligature to the appendix stump. Stump inversion was not carried out; it can be performed if required[47], even though there is good evidence from open surgery that it is not necessary[55].

As laparoscopic surgery develops one can envisage a plan of 'laparoscopy – possibly proceeding to laparoscopic appendicectomy'. The problem remains what to do when a normal appendix is seen and no other cause for the symptoms is found. As noted above, macroscopic assessment of the appendix may be unreliable[34], which might support its removal in these cases. However, the importance of minimal mucosal inflammation in a normal-looking appendix is debatable and probably does not justify appendicectomy in all equivocal cases. The possible advantages of laparoscopic appendicectomy over the open procedure with regard to operating time and postoperative stay remain unclear despite prospective study[56,57]. However, it would appear that follow-up laparoscopy after both open and laparoscopic appendicectomy reveals a much lower incidence of adhesions in the latter group (two of 20 *versus* 16 of 20)[58].

Perforated peptic ulcer

Perforated peptic ulcer is another condition for which the laparoscopic approach has attractions. It has been well established that some patients with perforated ulcer can be successfully managed by non-operative means[59] and, for many of those who do require operation, peritoneal toilet is often the only treatment required, the perforation having been sealed by omentum. Early reports of laparoscopic treatment of perforated ulcer have shown that not only can peritoneal toilet be performed effectively but perforations may also be closed[60,61] by intraperitoneal sutures or fibrin sealants to secure the omental plug. Concomitant gastroscopy permits the ulcer to be visualized from 'within', and by passing a Dormia basket through the perforation a plug of omentum can be drawn into the defect[46]. If at laparoscopy the perforation appears to have sealed spontaneously, peritoneal toilet alone would seem reasonable. Confirmation of insignificant leakage can be made by preoperative contrast studies[62] or intraoperative infusion of dyes, such as methylene blue, down a nasogastric tube.

Acute diverticular disease

There have been few reports of the use of therapeutic laparoscopy for acute diverticulitis. Diagnostic laparoscopy provides excellent information regarding the state of diverticular disease[26] and, with current enthusiasm and success for laparoscopically assisted colectomy[63], it would not be unreasonable to expect similar techniques to be applied to acute diverticulitis. Preoperative information regarding a colonic leak can be obtained from a retrograde contrast enema[64] and would help the surgeon plan operative strategy pending laparoscopic inspection. A localized abscess without overt faecal soiling would be amenable to drainage under laparoscopic guidance. In cases of perforation requiring resection, the extent and severity of disease would determine how much is feasible using laparoscopy.

Intestinal obstruction and adhesiolysis

Adhesions are often divided at laparoscopy to improve access and exposure but whether this manoeuvre is therapeutic in patients with chronic pain is debatable[65]. The problems of using laparoscopy to divide adhesions in the presence of established intestinal obstruction are obvious and pneumoperitoneum should be achieved using the open technique. Although division of widespread intra-abdominal adhesions will not be possible using laparoscopy, selected patients with an isolated band may be suitable[46].

Acute cholecystitis

In the early period of laparoscopic cholecystectomy many surgeons excluded patients with acute cholecystitis but, in line with the trend in open surgery towards early cholecystectomy for this condition[66], reports of laparoscopic cholecystectomy for acute cholecystitis are now available. Although the rate of conversion to open operation is much higher than for non-acute cases (25 *versus* 4 per cent), the morbidity and mortality rates do not differ from those of the elective situation[67]. There is no doubt that a delayed elective laparoscopic cholecystectomy to remove a shrunken fibrosed and non-functioning gallbladder is much more difficult than it is to remove a functioning gallbladder[68]. Open operation may still be the most appropriate treatment when the gallbladder is frankly gangrenous, to prevent the much higher risk of rupture associated with laparoscopic mobilization and dissection.

Gynaecological emergencies

Gynaecological emergencies remain a common cause of admission to general surgical wards, in some series the incidence being as high as 13 per cent[69]. Laparoscopy has been used as a diagnostic procedure in gynaecological emergencies for many years but, with the exception of a few enthusiasts[70], once the diagnosis was established treatment was usually by laparotomy. This policy seems destined to change following a recent study from Oxford in which 49 women with gynaecological emergencies were managed with videolaparoscopy[71]. The laparoscopic procedure was successful in 45 and the mean postoperative hospital stay was 1·9 days. Twenty-four of 25 women with ectopic pregnancies and 14 of 15 with ovarian cysts were successfully treated by laparoscopic surgery. In a randomized controlled trial comparing open and laparoscopic surgery for the treatment of unruptured ectopic gestation, postoperative stay was much shorter following the closed procedure (1·4 *versus* 3·3 days), although safety and efficacy were the same[72]. Whether it is as easy to evaluate and perform tubal repair by the laparoscopic approach in favourable cases of ruptured ectopic pregnancy remains unproven. Other centres have also reported the successful laparoscopic treatment of ovarian cysts[73].

Conclusions

Emergency admissions continue to take up a large proportion of the overall general surgical workload and available resources in the UK[74]; incorporation of diagnostic and therapeutic laparoscopy is likely to have important cost benefits. It can now be confidently argued that laparoscopy should be routine in the management of patients with acute abdominal pain in whom the decision to operate is uncertain and in all women with suspected appendicitis, irrespective of the certainty with which the diagnosis is made, because of the high error rate in this group. The ability to perform many of the more common emergency procedures using laparoscopic techniques is now fairly widespread and the decision to proceed with therapeutic laparoscopy will depend on many factors, of which surgical experience and theatre logistics remain the most pertinent. Future studies must identify which laparoscopic procedures provide 'value for money'. Objectives must be well defined and a shorter postoperative hospital stay, although important, must not be seen as the ultimate goal. The possible reduction in complications such as chest infection and wound sepsis needs to be quantified, in addition to the requirements for postoperative analgesia and early return to normal activities, a factor neglected by many current studies. Length of operation may not be important in itself but must be taken in context with the emergency workload and the time available in the operating theatre. The recent trend to establish dedicated theatres so that emergency procedures need not be postponed until elective surgery has been completed[75] will further facilitate the introduction and availability of emergency laparoscopy.

Early reports on the laparoscopic treatment of perforated peptic ulcer[60] and acute appendicitis[53] do not show a dramatic reduction in postoperative stay and more information is required before these and other procedures can be recommended. Results from prospective trials of operations such as appendicectomy[76] are eagerly awaited. Early criticism[57] of some trials[56] for not comparing like with like because the experience of the operating surgeon differs for the open and laparoscopic procedures is valid but misplaced. It is equally important to study what happens in the real world and, as most open appendicectomies are performed by junior surgical staff, it is against these results that any new procedure should be compared. If laparoscopic appendicectomy performed by senior surgeons is shown to be superior to open appendicectomy performed by junior surgeons then, in addition to altering surgical practice, the problem of surgical training should be addressed[77].

Conditions causing acute abdominal pain for which laparoscopy with or without laparoscopic surgery has a potential role include acute appendicitis, acute gynaecological conditions, intestinal obstruction caused by band adhesions, acute diverticulitis, perforated peptic ulcer, acute cholecystitis, mesenteric infarction and disseminated malignancy presenting as acute abdominal pain. As diagnostic laparoscopy becomes more popular in the acute abdomen, so the opportunity to perform other emergency laparoscopic procedures will arise. In addition to the above procedures, small bowel resection, excision of Meckel's diverticulum, and closure of traumatic intestinal perforations are all possible using the laparoscope. However, their feasibility does not justify their practice outwith prospective studies at the present time.

References

1. Perissat J, Collet D, Belliard R. Gallstones: laparoscopic treatment – cholecystectomy, cholecystostomy and lithotripsy. *Surg Endosc* 1990; **4**: 1–5.
2. Adams ID, Chan M, Clifford PC *et al.* Computer aided diagnosis of acute abdominal pain: a multicentre study. *BMJ* 1986; **293**: 800–4.
3. Sutton GC. Computer-aided diagnosis: a review. *Br J Surg* 1989; **76**: 82–5.
4. Hoffmann J. Peritoneal lavage in the diagnosis of the acute

abdomen of non-traumatic origin. *Acta Chirurgica Scandinavica* 1987; **153**: 561–5.

5. Stewart RJ, Gupta RK, Purdie GL, Isbister WH. Fine-catheter aspiration cytology of peritoneal cavity improves decision-making about difficult cases of acute abdominal pain. *Lancet* 1986; **ii**: 1414–15.
6. Ooms HWA, Koumans RKJ, Ho Kang You PJ, Puylaert JBCM. Ultrasonography in the diagnosis of acute appendicitis. *Br J Surg* 1991; **78**: 315–18.
7. Sugarbaker PH, Bloom BS, Sanders JH, Wilson RE. Preoperative laparoscopy in diagnosis of acute abdominal pain. *Lancet* 1975; **i**: 442–5.
8. Irvin TT. Abdominal pain: a surgical audit of 1190 emergency admissions. *Br J Surg* 1989; **76**: 1121–5.
9. Irvin TT. Mortality of perforated peptic ulcer: a case for risk stratification in elderly patients. *Br J Surg* 1989; **76**: 215–18.
10. Moss JG, Barrie JL, Gunn AA. Delay in surgery for acute appendicitis. *J R Coll Surg Edinb* 1985; **30**: 290–3.
11. Hunter IC, Paterson JG, Davidson AI. Deaths from acute appendicitis: a review of twenty-one cases in Scotland from 1974–1979. *J R Coll Surg Edinb* 1986; **31**: 161–3.
12. Hoffmann J, Rasmussen OØ. Aids in the diagnosis of acute appendicitis. *Br J Surg* 1989; **76**: 774–9.
13. Chang FC, Hogle HH, Welling DR. The fate of the negative appendix. *Am J Surg* 1973; **126**: 752–4.
14. Deutsch AA, Shani N, Reiss R. Are some appendicectomies unnecessary? *J R Coll Surg Edinb* 1983; **28**: 35–40.
15. Anteby SO, Schenker JG, Polishuk WZ. The value of laparoscopy in acute pelvic pain. *Ann Surg* 1975; **181**: 484–6.
16. Leape LL, Ramenofsky ML. Laparoscopy for questionable appendicitis – can it reduce the negative appendicectomy rate? *Ann Surg* 1980; **191**: 410–13.
17. Anderson JL, Bridgewater FHG. Laparoscopy in the diagnosis of acute lower abdominal pain. *Aust N Z J Surg* 1981; **51**: 462–4.
18. Deutsch AA, Zelikovsky A, Reiss R. Laparoscopy in the prevention of unnecessary appendicectomies: a prospective study. *Br J Surg* 1982; **69**: 336–7.
19. Reiertsen O, Rosseland AR, Høivik B, Solheim K. Laparoscopy in patients admitted for acute abdominal pain. *Acta Chirurgica Scandinavica* 1985; **151**: 521–4.
20. Clarke PJ, Hands LJ, Gough MH, Kettlewell MG. The use of laparoscopy in the management of right iliac fossa pain. *Ann R Coll Surg Engl* 1986; **68**: 68–9.
21. Paterson-Brown S, Eckersley JRT, Sim AJWS, Dudley HAF. Laparoscopy as an adjunct to decision-making in the 'acute abdomen'. *Br J Surg* 1986; **73**: 1022–4.
22. Paterson-Brown S, Thompson JN, Eckersley JRT, Ponting GA, Dudley HAF. Which patient with suspected appendicitis should undergo laparoscopy? *BMJ* 1988; **296**: 1363–4.
23. Spirtos NM, Eisenkop SM, Spirtos TW, Poliakin RI, Hibbard LT. Laparoscopy – a diagnostic aid in cases of suspected appendicitis. Its use in women of reproductive age. *Am J Obstet Gynecol* 1987; **156**: 90–4.
24. Foster HMcA. Which patients should undergo laparoscopy? *BMJ* 1988; **297**: 489.
25. Paterson-Brown S. Strategies for reducing inappropriate laparotomy rate in the acute abdomen. *BMJ* 1991; **303**: 1115–18.
26. Paterson-Brown S. The acute abdomen: the role of laparoscopy. In: Williamson RCN, Thompson JN, eds. *Gastrointestinal Emergencies*. Part I. London: Baillière Tindall, 1991: 691–703.
27. Gomel V. Laparoscopy in general surgery. *Am J Surg* 1976; **131**: 319–23.
28. Sundal E, Gry K, Fahrlaender H. Peritoneoscopy in abdominal emergencies. A valuable diagnostic tool. *Endoscopy* 1982; **14**: 97–9.
29. Nagy AG, James D. Diagnostic laparoscopy. *Am J Surg* 1989; **157**: 490–3.
30. Gray DWR, Collin J. Non-specific abdominal pain as a cause of acute admission to hospital. *Br J Surg* 1987; **74**: 239–42.
31. Paterson-Brown S, Olufunwa SA, Galazka N, Simmons SC. Visualisation of the normal appendix at laparoscopy. *J R Coll Surg Edinb* 1986; **31**: 106–7.
32. Crichton D. Ultrasonography for diagnosing acute appendicitis. *BMJ* 1988; **297**: 857.
33. Whitworth CM, Whitworth PW, Sanfillipo J, Polk HC. Value of diagnostic laparoscopy in young women with possible appendicitis. *Surg Gynecol Obstet* 1988; **167**: 187–90.
34. Lau WY, Fan ST, Yiu TF, Chu KW, Suen HC, Wong KK. The clinical significance of routine histopathologic study of the resected appendix and safety of stump invagination. *Surg Gynecol Obstet* 1986; **162**: 256–8.
35. Wood JJ, Bolton JP, Cannon SR. Biliary-type pain as a manifestation of genital tract infection: the Curtis–Fitz-Hugh syndrome. *Br J Surg* 1982; **69**: 251–3.
36. Pearce JM. Pelvic inflammatory disease. *BMJ* 1990; **300**: 1090–1.
37. Iberti TJ, Salky BA, Onofrey D. Use of bedside laparoscopy to identify intestinal ischemia in postoperative cases of aortic reconstruction. *Surgery* 1989; **105**: 686–9.
38. Velanovitch V. Bayesian analysis of the reliability of peritoneal lavage. *Surg Gynecol Obstet* 1990; **170**: 7–11.
39. Lowe RJ, Boyd DR, Folk FA, Baker RJ. The negative laparotomy for abdominal trauma. *J Trauma* 1972; **12**: 853–61.
40. Estes WL. Nonpenetrating trauma of the abdomen. *Surg Gynecol Obstet* 1942; **70**: 419–24.
41. Gazzaniga AB, Stanton WW, Bartlett RH. Laparoscopy in the diagnosis of blunt and penetrating injuries to the abdomen. *Am J Surg* 1976; **131**: 315–23.
42. Sherwood R, Berci G, Austin E, Morgenstern L. Minilaparoscopy for blunt abdominal trauma. *Arch Surg* 1980; **115**: 672–3.
43. Berci G, Dunkelman D, Michel SL, Sanders G, Wahlstrom E, Morgenstern L. Emergency minilaparoscopy in abdominal trauma. *Am J Surg* 1983; **146**: 261–5.
44. Cuschieri A, Hennessy TPJ, Stephens R, Berci G. Diagnosis of significant abdominal trauma after road traffic accidents: preliminary results of a multicentre trial comparing minilaparoscopy with peritoneal lavage. *Ann R Coll Surg Engl* 1988; **70**: 153–5.
45. Adamthwaite DN. Traumatic diaphragmatic hernia: a new indication for laparoscopy. *Br J Surg* 1984; **71**: 315.
46. Perissat J, Collet D, Edye M. Therapeutic laparoscopy. *Endoscopy* 1992; **24**: 138–43.
47. Semm K. Endoscopic appendicectomy. *Endoscopy* 1983; **15**: 59–64.
48. Schreiber JH. Early experience with laparoscopic appendicectomy in women. *Surg Endosc* 1987; **1**: 211–16.
49. Gangal HT, Gangal MH. Laparoscopic appendicectomy. *Endoscopy* 1987; **19**: 127–9.
50. Leahy PF. Technique of laparoscopic appendicectomy. *Br J Surg* 1989; **76**: 616.
51. Fleming JS. Laparoscopically directed appendicectomy. *Aust N Z J Obstet Gynaecol* 1985; **25**: 238–40.
52. Byrne DS, Bell G, Morrice JJ, Orr G. Technique for laparoscopic appendicectomy. *Br J Surg* 1992; **79**: 574–5.
53. Pier A, Gotz F, Bacher C. Laparoscopic appendectomy in 625 cases: from innovation to routine. *Surgical Laparoscopy and Endoscopy* 1991; **1**: 8–13.
54. Valla JS, Limmone B, Valla V *et al.* Laparoscopic appendectomy in children: report of 465 cases. *Surgical Laparoscopy and Endoscopy* 1991; **1**: 166–72.
55. Engstrom L, Fenyo G. Appendicectomy: assessment of stump invagination – a prospective, randomized trial. *Br J Surg* 1985; **72**: 971–2.
56. McAnena OJ, Austin O, Hederman WP, Gorey TF, Fitzpatrick J, O'Connell PR. Laparoscopic *versus* open appendicectomy. *Lancet* 1991; **338**: 693 (Letter).
57. Banerjee AK. Laparoscopic appendicectomy. *Lancet* 1991; **338**: 893 (Letter).
58. De Wilde RL. Goodbye to late bowel obstruction after appendicectomy. *Lancet* 1991; **338**: 1012 (Letter).
59. Crofts TJ, Park KGM, Steele RJC, Chung SSC, Li AKC. A randomized trial of non-operative treatment for perforated peptic ulcer. *N Engl J Med* 1989; **320**: 970–3.
60. Mouret P, Francois Y, Vignal J, Barth X, Lombard-Platet R. Laparoscopic treatment of perforated peptic ulcer. *Br J Surg* 1990; **77**: 1006.
61. Nathanson LK, Easter DW, Cuschieri A. Laparoscopic repair/peritoneal toilet of perforated duodenal ulcer. *Surg Endosc* 1990; **4**: 232–3.
62. Ott DJ, Gelfand DW. Gastrointestinal contrast agents: indications, uses and risks. *JAMA* 1983; **249**: 2380–4.
63. Schlinkert RT. Laparoscopic-assisted right hemicolectomy. *Dis Colon Rectum* 1991; **34**: 1030–1.
64. Kourtesis GJ, Williams SE. Acute diverticulitis: safety and value of contrast studies in predicting need for operation. *Aust N Z J Surg* 1988; **58**: 801–4.
65. Alexander-Williams J. Do adhesions cause pain? *BMJ* 1987; **294**: 659–60.
66. Addison NV, Finan PJ. Urgent and early cholecystectomy for acute gall bladder disease. *Br J Surg* 1988; **75**: 141–3.
67. Domergue J, Fabre JM, Guillon F *et al.* Laparoscopic cholecystectomy in acute and non-acute cholecystolithiasis. *Research in Surgery* 1991; **3**: 147–9.

68. Nathanson LK, Shimi S, Cuschieri A. Laparoscopic cholecystectomy: the Dundee technique. *Br J Surg* 1991; **78**: 155–9.
69. Paterson-Brown S, Eckersley JRT, Dudley HAF. The gynaecological profile of acute general surgery. *J R Coll Surg Edinb* 1988; **33**: 13–15.
70. Semm K. Operative pelviscopy. *Br Med Bull* 1986; **42**: 284–95.
71. Magos AL, Baumann R, Turnbull AC. Managing gynaecological emergencies with laparoscopy. *BMJ* 1989; **299**: 371–4.
72. Vermesh M, Silva PD, Rosen GF, Stein AL, Fossum GT, Sauer MV. Management of unruptured ectopic gestation by linear salpingostomy: a prospective, randomized clinical trial of laparoscopy *versus* laparotomy. *Obstet Gynecol* 1989; **73**: 400–3.
73. Hasson HM. Laparoscopic management of ovarian cysts. *J Reprod Med* 1990; **35**: 863–7.
74. Ellis BW, Rivett RC, Dudley HAF. Extending the use of clinical audit data: a resource planning model. *BMJ* 1990; **301**: 159–62.
75. Lunn JN, Devlin HB. Lessons from the confidential enquiry into perioperative deaths in three NHS regions. *Lancet* 1987; **ii**: 1384–6.
76. Loh A, Taylor RS. Laparoscopic appendicectomy. *Br J Surg* 1992; **79**: 289–90.
77. Jones PF. NCEPOD: more training needed. *BMJ* 1992; **304**: 1510 (Letter).

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Announcement

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Elective lymph node dissection in the management of malignant melanoma

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The surgical management of regional nodes in patients with cancer has been controversial for many years. This paper reviews the role of elective lymph node dissection in the management of malignant melanoma. The evidence for and against elective lymphadenectomy is discussed and a policy of therapeutic, rather than elective, lymph node excision recommended.

The role of elective lymph node dissection (ELND) in the management of malignant melanoma is controversial. This issue is important for surgeons involved in management of cutaneous malignant melanoma and raises questions about interpretation of the natural history of the disease and motives for surgical intervention. If regional nodes are clinically involved, therapeutic block dissection is indicated[1–3]; there is no debate about this. The issue that divides the surgical community centres on the surgical management of the patient with primary malignant melanoma without evidence of clinically involved regional nodes. Pemberton, in 1858, advocated a wide deep excision for primary lesions plus excision of the regional nodes if involved[4]. A year after the influential 1907 publication of Sampson Handley[5], Hogarth Pringle[6] introduced the radical in-continuity excision of primary lesion, intervening skin, lymphatics and regional nodes, whether involved or not. This type of excisional surgery for cancer found favour with the generation of surgeons who practised Halsted's radical mastectomy for breast cancer.

This review deals mainly with the management of regional nodes draining the limbs because limb primaries are common, lymphatic drainage is predictable and major studies have concentrated on this aspect.

Rationale for elective lymphadenectomy

Even the strongest supporters of ELND agree that only a selected group of patients may benefit from the procedure[3,7]. Balch and Milton favoured elective intervention, whereas Cascinelli and Sim advocated dissection of nodes when they became clinically involved, i.e. therapeutic lymphadenectomy[7]. In a recent review, Balch restated his position but presented no new evidence[3]. The rationale for elective dissection is based on the hypothesis that cutaneous malignant melanoma spreads, in a stepwise manner, from the primary to the regional nodes and then to distant sites[3]. If this is true, then patients with occult micrometastases in the regional nodes should benefit from elective lymphadenectomy, because it is performed when the tumour burden is small and before systemic spread occurs. By the time clinically detectable nodal metastases are established, most patients (70–85 per cent) will already have distant micrometastases and the 10-year survival rate is around 25 per cent[8]. The aim of ELND is, therefore, to provide definitive surgical treatment at an early stage in the natural history of the disease. Balch and Milton contend that the Breslow thickness of the primary melanoma is the major indicator of the group of patients who might benefit most from ELND[7]. They argue that primary melanoma of Breslow thickness 0·76–4 mm has a high risk of occult regional metastases, up to 60 per cent in patients with lesions 1·5–4·99 mm thick[3], and a low risk of systemic metastases and that such patients should benefit from elective lymphadenectomy[9–13].

There has been discussion in the literature about the extent and timing of ELND. There is no evidence to confirm whether inguinal or ilioinguinal dissection is more appropriate in the management of lower-limb disease. The major proponents of ELND perform an inguinal procedure[3,13] and the iliac glands are spared unless the inguinal nodes are found to contain metastases. It has been argued that lymphatic stasis, which is common after elective lymphadenectomy, may provide a favourable environment for the survival and proliferation of melanoma cells[14]. Furthermore, immediate ELND may result in the seeding in transit of intralymphatic cells that might otherwise reach and be contained by the draining nodes, a mechanism that provides a rationale for 'interval' elective dissection. Petersen and colleagues[15] found that interval ELND, i.e. delayed >14 days after primary excision, was associated with a lower incidence of locoregional recurrence. Wanebo *et al.*[16] and McCarthy and colleagues[14] found no benefit from similar approaches and the only prospective study that addresses this question is too small to provide a definitive answer[17]. In the absence of good evidence in favour of interval ELND, those who carry out elective lymphadenectomy tend to do so along with definitive excision of the primary lesion under a single general anaesthetic[7].

Evidence for and against elective lymph node dissection

The main studies for and against ELND are summarized in *Tables 1* and *2*. Where a series has been updated, the most recent data are used.

The theory invoked in favour of elective lymphadenectomy is attractive but there are important objections to it. First, although the regional nodal basin is the most common site of first metastasis[27,28], malignant melanoma does not always spread via the regional lymph nodes. Balch's contention that Breslow thickness allows prediction of the site of metastasis[3,11,29] has not been confirmed. In a World Health Organization (WHO) study of 1164 stage I patients treated without elective dissection, 516 suffered a relapse within 10 years of treatment; of these, 51 per cent presented with first recurrence in the regional nodes, 22 per cent with distant metastases and 31 per cent with simultaneous regional lymphatic and distant metastases[30]. Evidence is emerging that may explain why, in both malignant melanoma and breast cancer[31], treatment of the regional lymph nodes fails to influence survival. It is now known that lymphovenous anastomoses often bypass nodes and there are naturally occurring channels that allow intact cells to pass through lymph nodes[32,33]. Thus, cancer cells may disseminate simultaneously by the bloodstream and lymphatic pathways; lymph node

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Table 1 *Studies quoted as evidence in favour of elective lymphadenectomy in the management of clinical stage I malignant melanoma*

Reference	Year	Study design	Follow-up (years)	No. of patients	Site	No. of excisions alone	No. of ELND procedures	Metastases in excised nodes (%)	Possible benefit from ELND	Morbidity from ELND	Mortality from ELND
Milton *et al.*[12]	1982	Single centre, retrospective non-randomized	2–32	1319	All	939	380	5	Men with limb lesion 1·6–3 mm thick	'Acceptably low'	2 deaths
Balch *et al.*[10]	1982	Part prospective	2–25	1356	All	865	491	—	All 1·3–3·99 mm thick; men 0·76–1·5 mm thick	—	—
McCarthy *et al.*[18]	1985	Single centre, part prospective	10	2347	Trunk and limb	1719	628	4	All 1·6–3 mm thick	—	—
Reintgen *et al.*[13]	1983	Regional centre, retrospective	2–10	613	Trunk and limb*	426	187	—	Borderline	—	—
Fortner *et al.*[19]	1977	Regional centre, retrospective	5–10	404	Trunk and limb	145	259	15	6 of 9 with micro-metastases survived 10 years	—	—
Wanebo *et al.*[16]	1975	Retrospective	5–9	151	Limb	38	113	12·4	?Clark level III	—	—
McCarthy *et al.*[20]	1988	Regional centre, retrospective	9·8	3171	All	2417	754	—	Breslow thickness >1·5 mm	—	—
Shaw *et al.*[21]	1987	Regional centre, retrospective	>10 in 34%	846	All†	784	62	0	?ulcerated, high mitotic rate, Clark level III or IV	—	—

ELND, elective lymph node dissection. *0·76–4 mm in thickness; † <0·76 mm in thickness

Table 2 *Studies quoted as evidence against elective lymphadenectomy in the management of clinical stage I malignant melanoma*

Reference	Year	Study design	Follow-up (years)	No. of patients	Site	No. of excisions alone	No. of ELND procedures	Metastases in excised nodes (%)	Possible benefit from ELND	Morbidity from ELND	Mortality from ELND
Veronesi *et al.*[22]	1982	Multicentre, prospective randomized	Mean 10·4	553	Distal two-thirds of limb	286	267	19·7	—	—	—
Sim *et al.*[23]	1986	Single centre, prospective randomized	Median 4·5	171	Trunk and limb	62	54 immediate, 55 delayed	—	None	Lymphoedema (32 of 109), seroma (15 of 109), poor healing (7 of 109)	0
Crowley and Seigler[24]	1990	Regional centre, retrospective	Median 6·7	308	All*	192	116	27·6	None	—	—
Karakousis *et al.*[25]	1987	Regional centre, retrospective	5–20	201	All	102	99	—	None	—	—
Binder *et al.*[26]	1990	Regional centre, retrospective	Mean 6	168	All	102	66	—	None	—	—

ELND, elective lymph node dissection. *4–10 mm in thickness metastases can be considered 'indicators, but not governors' of survival[32]. Furthermore, the demonstration of circulating malignant cells[34], nodal malignant cells[31] and even distant micrometastases[35] is not invariably associated with clinical metastases or death; there may be no inevitable advantage from excising nodes containing micrometastases. The major prognostic determinants of primary melanoma (for example, Breslow thickness) can identify patients at risk of metastases and death, but these criteria do not accurately predict the site of recurrence[30,36]. In the study of Milton *et al.* of the site and time of first recurrence after wide excision alone for stage I disease[28], a number of patients who developed first recurrences at multiple sites were excluded and a significant minority presented first with distant metastases.

Second, clinical stage I/pathological stage II disease (microscopic nodal metastases) is not directly comparable with clinical stage II (macroscopic, clinically apparent nodal metastases). Protagonists of ELND often argue[3,12] that the prognosis of patients who have microscopic regional nodal metastases, diagnosed after elective lymphadenectomy, is better than that of those who undergo therapeutic node dissection for clinically apparent nodal metastases. However, it is not surprising that there is a survival advantage for patients with a microscopic tumour burden compared with those with a clinically obvious malignant lymphadenopathy; it has even been shown that the number of involved nodes is itself of prognostic value[37]. Although the overall survival figures for patients undergoing ELND seem favourable (*Table 1*), it does not follow logically that such dissection benefits all those who undergo the operation. This is because many such patients undergo unnecessary operation as the excised glands have no demonstrable metastases and prognosis would have been good in any case. Conversely, those who have therapeutic dissection all have clinically apparent nodal metastases and the comparatively poor prognosis is related to the stage of disease.

A third objection to ELND comes from the two major prospective randomized studies that addressed the question of routine elective lymphadenectomy; both have shown no benefit from the procedure[17,22,23,38] (*Table 2*). Even the strongest advocates of elective excision agree with the principal finding, that not all patients with melanoma will benefit from the procedure[3,7]. Using the WHO data, Balch[3] argued that, because 56 per cent of patients treated by excision alone for lesions of Breslow thickness 1·5–4·99 mm subsequently required therapeutic lymph node dissection, this figure gives an estimate of the true incidence of microscopic nodal metastases at the time of treatment of the primary lesion. The fallacy in this argument is that there is no reason to suppose that all subsequent nodal disease is the result of micrometastases present in nodes at or before the time of treatment of the primary. At least a proportion of nodal metastases develop as a result of delayed spread from locoregional or distant sites. Balch's theory is historically based on the 42 per cent incidence of occult nodal metastases in ELND specimens serially sectioned and reported in retrospective studies by Lane and colleagues[39] in 1958 and Das Gupta[40] in 1977.

In the Mayo Clinic trial of elective lymphadenectomy, the incidence of microscopic nodal metastases was 6 per cent overall[23]; in the WHO study the incidence was 19·7 per cent overall and only 21 per cent in the intermediate thickness group[22] (*Table 2*). In the latter trial 24·2 per cent of patients having excision of the primary alone developed nodal metastases[22,38] in a 5-year follow-up period. Importantly, there was no significant difference in 5-year survival rate between this subgroup and that treated by ELND.

The data from both the WHO[22] and Mayo Clinic[23] studies support therapeutic node dissection when required, as opposed to a routine elective procedure. These major prospective studies of ELND were concerned mainly with the general applicability of the operation and neither the WHO[22,38] nor Mayo Clinic[17,23] trial was designed to determine whether specific small subgroups might benefit. In the latter study[17,23] there were few patients in the categories that Balch and colleagues consider likely to benefit from ELND.

The WHO Melanoma Group study[38] was initiated before the identification of factors now recognized to be of considerable prognostic significance: neither Breslow thickness nor ulceration was originally included in the stratification criteria. Balch has indicated that, although tumour thickness is divided evenly between the treatment arms in the WHO study[3], in the group of intermediate thickness (1·5–4·99 mm) there was a higher incidence of ulceration in those undergoing ELND (52 per cent) than in those having wide excision alone (19 per cent). However, <10 per cent of the study population fell into this subgroup of patients having elective lymphadenectomy and the 'maldistribution' occurred at random. Balch stated that in this small highly selected group there may be a survival advantage from ELND[3,7] after accounting for ulceration. Even if this advantage in the 20 per cent with intermediate thickness lesions is real, it represents only a 4 per cent improvement in the whole group, of whom a majority would have been subjected to unnecessary surgery.

Some would extend the indications for elective lymphadenectomy to include primary melanoma of >4 mm Breslow thickness[41]. A recent retrospective study of 308 patients with clinical stage I melanoma (4–10 mm) showed no benefit from ELND and the authors concluded that the risk of distant metastases outweighs any benefit of the procedure[24]. In another retrospective study there was no advantage from elective lymphadenectomy in any Breslow thickness group[26].

The risks of mortality and morbidity associated with the additional surgical intervention of ELND should not be forgotten. There were two deaths in the Sydney experience of elective excision[12], probably occurring in the early years of the operation, but it would be difficult to justify any adjuvant treatment with a significant risk of mortality today. ELND is also associated with morbidity. In a series of 58 patients from Birmingham, Alabama[1,42], 26 per cent developed lymphoedema after inguinal node dissection, 23 per cent seroma, 5 per cent wound infection, 5 per cent persistent pain and 8 per cent persistent 'functional deficit'. In the UK, Bowsher and colleagues[43] reported one death in a series of 46 patients undergoing inguinal node dissection for malignant melanoma: 35 per cent developed seroma and 30 per cent wound infection.

It must be acknowledged that there may be deficiencies in the two prospective randomized trials of elective lymphadenectomy. The multicentre nature of the WHO trial may have led to variability in standardization of clinical staging and surgical treatment[3,7]. Another criticism of this trial is that, since only limb lesions were selected for study, 85 per cent of the patients were women. A population at particularly low risk of metastases may thereby have been selected and the overall good prognosis might have diluted any benefit from ELND. However, Breslow and Geelhoed[44] compared the mortality rates of patients in this study with those from the series of Wanebo and colleagues[16], in which there was twice the proportion of men. This comparison showed that, thickness for thickness, there was no significant difference in survival between patients in the two studies.

In both prospective trials there was careful follow-up of the group managed by wide local excision alone, to facilitate the early detection of regional lymph node metastases. However, clinical accuracy in the diagnosis of metastatic nodes is poor. Gumport and Harris[45] noted clinical underdiagnosis of 29 per cent of patients (clinically negative but histologically positive) and overdiagnosis in 23 per cent. Fine-needle aspiration cytology or open biopsy may be helpful when the clinical findings are equivocal[1].

In the WHO trial the overall 10-year survival rate was 15–20 per cent for patients needing subsequent therapeutic node dissection[22]. Those with a single positive node at therapeutic excision had a 44 per cent 10-year survival rate, which is an incentive to the early detection and treatment of nodal metastases when ELND is not practised. The studies performed by Balch, Milton and others, and cited by them in favour of elective lymphadenectomy[3,7,10,12], are described in later publications as 'prospective but non-randomized' trials. On careful inspection it is clear that in both the Alabama and Sydney series a significant proportion of the data was retrospectively culled from case records, and in the 'prospective' parts of these studies the criteria that were used to select patients for ELND are not clearly defined. The University of Alabama melanoma registry[10] began in 1975 but includes patients treated since 1955; the Sydney study includes patients treated between 1950 and 1980. This retrospective cohort is acknowledged as such in an early publication[12] but is included with a prospective cohort in later papers[1,3,7,10].

Breslow and Geelhoed[44] indicated that the literature concerning ELND from before 1977, including some of Breslow's own work, is difficult to evaluate because the studies were retrospective and liable to bias in patient selection. Breslow found, on reanalysing the data from his 1975 paper[46], that surgical colleagues had been selecting patients for ELND who had limb rather than axial lesions, which have a less predictable lymphatic drainage. In addition, none of the patients with Clark level V lesions underwent elective excision. Inadvertently the surgeons had selected for ELND those patients with the best prognosis.

This kind of problem appears again in the retrospective study of Reintgen and colleagues[13] (*Table 1*) in which patients were referred by 30 different surgeons for adjuvant therapy after initial surgery. A minority of patients actually underwent ELND and there was a bias towards elective lymphadenectomy for limb lesions. As in the work of Milton *et al.*, the problem of selection bias was dealt with partly by retrospective analysis of the patient groups after stratification according to dominant prognostic indicators revealed by multifactorial analysis[12]. Statistically, this is less satisfactory than prospective randomization with stratification. None of these studies can deal with the improvement in prognosis that has occurred in recent successive decades.

Such criticisms do not render the studies supporting ELND null and void but serve to emphasize that conscious and unconscious bias can corrupt retrospective analyses. An alternative position for the supporters of elective excision would be to present the truly prospective parts of their series as separate trials, since presumably selection criteria were used to allocate patients to the different treatments. To date, this information is not available.

Conclusions

The evidence of the two major prospective randomized studies to date suggests that there is no overall survival advantage conferred by elective lymphadenectomy. A fuller answer to this problem should emerge from the trials of ELND in subgroups of patients with stage I melanoma that have been activated by the National Cancer Institute of the USA (primary melanoma 1–4 mm Breslow thickness) and WHO Melanoma Group (trunk lesions >2 mm Breslow thickness). Until the results of these studies become available, the clinician must manage patients on the basis of personal interpretation of the available evidence.

ELND cannot be undertaken without risk of significant morbidity from lymphoedema and wound infection. Many patients undergoing elective lymphadenectomy will not need this procedure. Any advantage from ELND is likely to be small, even in selected subgroups. It is, therefore, reasonable to pursue a policy of therapeutic rather than elective lymphadenectomy.

There is no evidence from the trials discussed that the removal of healthy nodes confers any advantage or disadvantage to the patient with malignant melanoma. If there were an effective adjuvant therapy for cutaneous malignant melanoma then, as in breast cancer, ELND might be justified as a sampling procedure for staging. Finally, it is important to note that if a policy of therapeutic node dissection is practised then, as in the WHO and Mayo Clinic trials, patients will require long-term follow-up to allow early detection and treatment of any regional nodal metastases that develop.

References

1. Balch CM, Urist MM, Maddox WA, Milton GW, McCarthy WH. Management of regional metastatic melanoma. In: Balch CM, Milton GW, eds. *Cutaneous Melanoma. Clinical Management and Treatment Results World-wide.* Philadelphia, Pennsylvania: JB Lippincott, 1985: 93–130.
2. Rosin RD. The treament of malignant melanoma. *Eur J Surg Oncol* 1985; **11**: 111–15.
3. Balch CM. The role of elective lymph node dissection in melanoma: rationale, results and controversies. *J Clin Oncol* 1988; **6**: 163–72.
4. Pemberton O. *Observations on the History, Pathology and Treatment of Cancerous Diseases.* London: Churchill, 1858.
5. Sampson Handley W. The pathology of melanotic growths in relation to their operative treatment. *Lancet* 1907; **i**: 927–33, 996–1003.
6. Hogarth Pringle J. A method of operation in cases of melanotic tumours of the skin. *Edinburgh Medical Journal* 1908; **23**: 496–9.
7. Balch CM, Cascinelli N, Milton GW, Sim FH. Elective lymph node dissection: pros and cons. In: Balch CM, Milton GW, eds. *Cutaneous Melanoma. Clinical Management and Treatment Results World-wide.* Philadelphia, Pennsylvania: JB Lippincott, 1985: 131–57.
8. Balch CM, Soong SJ, Murad TM, Ingalls AL, Maddox WA. A multifactorial analysis of melanoma. III. Prognostic factors in melanoma patients with lymph node metastases (stage II). *Ann Surg* 1981; **193**: 377–88.
9. Balch CM, Murad TM, Soong S, Ingalls AL, Halpern NB, Maddox WA. A multifactorial analysis of melanoma: prognostic histopathological features comparing Clark's and Breslow's staging methods. *Ann Surg* 1978; **188**: 732–42.
10. Balch CM, Soong S, Milton GW *et al.* A comparison of prognostic factors and surgical results in 1786 patients with localised (stage I) melanoma treated in Alabama, USA, and New South Wales, Australia. *Ann Surg* 1982; **196**: 677–84.
11. Balch CM, Murad T, Soong S, Ingalls AL, Richards PC, Maddox WA. Tumour thickness as a guide to surgical management of clinical stage I melanoma patients. *Cancer* 1979; **43**: 883–8.
12. Milton GW, Shaw HM, McCarthy WH, Pearson L, Balch CM, Soong S. Prophylactic lymph node dissection in clinical stage I cutaneous malignant melanoma: results of surgical treatment in 1319 patients. *Br J Surg* 1982; **69**: 108–11.
13. Reintgen DS, Cox EB, McCarty KS, Vollmer RT, Seigler HF. Efficacy of elective node dissection in patients with intermediate thickness primary melanoma. *Ann Surg* 1983; **198**: 379–85.
14. McCarthy JG, Haagensen CD, Hertel FP. The role of groin dissection in the management of melanoma of the lower extremity. *Ann Surg* 1974; **179**: 156–9.
15. Petersen NC, Bodenham DC, Lloyd OC. Malignant melanomas of the skin. A study of the origin, development, aetiology, spread, treatment and prognosis. Part II. *Br J Plast Surg* 1962; **15**: 97–116.
16. Wanebo J, Woodruff J, Fortner JG. Malignant melanoma of the extremities: a clinicopathologic study using levels of invasion (microstage). *Cancer* 1975; **35**: 666–76.
17. Sim FH, Taylor WF, Ivins JC, Pritchard DJ, Soule EH. A prospective randomised study of the efficacy of routine elective lymphadenectomy in management of malignant melanoma: preliminary results. *Cancer* 1978; **41**: 948–51.
18. McCarthy WH, Shaw HM, Milton GW. Efficacy of elective node dissection in 2347 patients with clinical stage I malignant melanoma. *Surg Gynecol Obstet* 1985; **161**: 575–80.
19. Fortner JG, Woodruff J, Schottenfeld D, MacLean B. Biostatistical basis of elective node dissection for malignant melanoma. *Ann Surg* 1977; **186**: 101–3.
20. McCarthy WH, Shaw HM, Thompson JF, Milton GW. Time and frequency of recurrence of cutaneous stage I malignant melanoma with guidelines for follow-up study. *Surg Gynecol Obstet* 1988; **166**: 497–502.
21. Shaw HM, McCarthy WH, McCarthy SW, Milton GW. Thin malignant melanomas and recurrence potential. *Arch Surg* 1987; **122**: 1147–50.
22. Veronesi U, Adamus J, Bandiera DC *et al.* Delayed regional lymph node dissection in stage I melanoma of the skin of the lower extremities. *Cancer* 1982; **49**: 2420–30.

23. Sim FH, Taylor WF, Pritchard DJ, Soule EH. Lymphadenectomy in the management of stage I malignant melanoma: a prospective randomised study. *Mayo Clin Proc* 1986; **61**: 697–705.
24. Crowley NJ, Seigler HF. The role of elective lymph node dissection in the management of patients with thick cutaneous melanoma. *Cancer* 1990; **66**: 2522–7.
25. Karakousis CP, Kachrimanidis S, Rao U, Emrich LJ. Changes in survival with clinical stage I malignant melanoma. *J Surg Oncol* 1987; **34**: 155–9.
26. Binder M, Pehamberger H, Steiner A, Wolff K. Elective regional lymph node dissection in malignant melanoma. *Eur J Cancer Clin Oncol* 1990; **26**: 871–3.
27. Cascinelli N, Bufalino R, Marolda R *et al.* Regional non-nodal metastases of cutaneous melanoma. *Eur J Surg Oncol* 1986; **12**: 175–80.
28. Milton GW, Shaw HM, Farago GM, McCarthy WH. Tumour thickness and the site and time of first recurrence in cutaneous malignant melanoma (stage I). *Br J Surg* 1980; **67**: 543–6.
29. Balch CM, Wilkerson JA, Murad TM, Soong SJ, Ingalls AL, Maddox WA. The prognostic significance of ulceration of cutaneous melanoma. *Cancer* 1980; **45**: 3012–17.
30. Cascinelli N, Preda F, Vaglini M *et al.* Metastatic spread of stage I melanoma of the skin. *Tumori* 1983; **69**: 449–54.
31. Fisher B. Biological and clinical considerations regarding the use of surgery and chemotherapy in the treatment of primary breast cancer. *Cancer* 1977; **40**: 574–87.
32. Cady B. Lymph node metastases: indicators, but not governors of survival. *Arch Surg* 1984; **119**: 1067–72.
33. Cady B. 'Prophylactic' lymph node dissection in melanoma: does it help? *J Clin Oncol* 1988; **6**: 2–4.
34. Roberts SS, Hengesh JW, McGrath RG *et al.* Prognostic significance of cancer cells in the circulating blood: a ten year evaluation. *Am J Surg* 1969; **113**: 757–62.
35. Weiss L, Glaves D, Waite DA. The influence of host immunity on the arrest of circulating cancer cells, and its modification by neuraminidase. *Int J Cancer* 1974; **13**: 850–62.
36. Van der Esch EP, Cascinelli N, Preda F, Morabito A, Bufalino R. Stage I melanoma of the skin: evaluation of prognosis according to histologic characteristics. *Cancer* 1981; **48**: 1668–73.
37. Balch CM, Soong S, Shaw HM, Milton GW. An analysis of prognostic factors in 4000 patients with cutaneous melanoma. In: Balch CM, Milton GW, eds. *Cutaneous Melanoma. Clinical Management and Treatment Results World-Wide.* Philadelphia, Pennsylvania: JB Lippincott, 1985: 321–52.
38. Veronesi U, Adamus J, Bandiera DC *et al.* Inefficacy of immediate node dissection in stage I melanoma of the limbs. *N Engl J Med* 1977; **297**: 627–30.
39. Lane N, Lattes R, Malm J. Clinico-pathological correlation in a series of 117 malignant melanomas of the skin of adults. *Cancer* 1958; **11**: 1025–43.
40. Das Gupta TK. Results of treatment of 269 patients with primary cutaneous melanoma: a five-year prospective study. *Ann Surg* 1977; **186**: 201–9.
41. Schneebaum S, Briele HA, Walker MJ *et al.* Cutaneous thick melanoma. Prognosis and treatment. *Arch Surg* 1987; **112**: 707–11.
42. Urist MM, Maddox WA, Kennedy JE, Balch CM. Patient risk factors and surgical morbidity after regional lymphadenectomy in 204 melanoma patients. *Cancer* 1983; **51**: 2152–6.
43. Bowsher WG, Taylor BA, Hughes LE. Morbidity, mortality and local recurrence following regional node dissection for melanoma. *Br J Surg* 1986; **73**: 906–8.
44. Breslow A, Geelhoed GW. Tumour thickness as a guide to treatment in cutaneous melanoma. In: Ariel IM, ed. *Malignant Melanoma.* New York: Appleton–Century–Crofts, 1981: 109–18.
45. Gumport SL, Harris MN. Results of regional lymph node dissection for melanoma. *Ann Surg* 1974; **179**: 105–8.
46. Breslow A. Tumour thickness, level of invasion and node dissection in stage I cutaneous melanoma. *Ann Surg* 1975; **182**: 572–5.

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Cytokines, sepsis and immunomodulation

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Tissue injury and infection produce significant alterations in host metabolic and immune homoeostasis. It is increasingly clear that many of these changes result from a complex cascade of mononuclear phagocyte-derived endogenous mediators. Among the more important is a group of host proteins called cytokines, which play an integral role in mediating the host response to tissue injury and infection. Of these proteins, tumour necrosis factor (TNF) and interleukin (IL) types 1 and 6 have received much attention for their pathophysiological roles in infection and trauma. Evidence is reviewed for the involvement of these cytokines in the characteristic alterations in the metabolic and immune responses to such injury. These endogenous mediators initiate an integrated fuel substrate and hormonal adjustment to trauma and sepsis, and help to provide optimal metabolic homoeostasis for systemic host defences. Widespread tissue injury, especially when associated with fulminant sepsis, may, however, precipitate massive release of TNF, IL-1 and IL-6, triggering a series of reactions involving multiple organs, and culminating in the 'sepsis syndrome'. New therapies designed to downregulate this aberrant response, either by neutralizing endotoxin directly or by blocking the release or actions of these cytokines, are reviewed. Although these treatments hold much promise for the future management of severely traumatized and infected patients, careful evaluation of both the benefits and complications of therapy is needed before widespread clinical use can be recommended.

Surgical, traumatic and thermal injury commonly stimulate a cascade of events that mediate major immune, haematological and metabolic alterations in the host response to insult. Recent evidence suggests that many of these changes are mediated by mononuclear phagocyte*-derived inflammatory mediators[1]. Activation of these cells is one of the earliest cellular responses to tissue injury and is associated with the release of a variety of inflammatory mediators including cytokines, arachidonic acid metabolites, complement split products, lysosomal enzymes and oxygen free radicals. Mononuclear phagocyte-derived cytokines specifically mediate, via both paracrine and endocrine mechanisms, the non-specific host defence and metabolic response to tissue injury and infection. They do this by stimulating the mobilization of oxygen transport, energetic substrate and amino acids, while also promoting protein synthesis and cellular proliferation in the liver, bone marrow, wound and immune system.

Major tissue injury, especially when associated with infection, is commonly attended by widespread and uncontrolled activation of the mononuclear phagocyte cell population. This process is responsible for the release of massively increased quantities of several inflammatory mediators that spill over into the general circulation to exert systemic effects, collectively constituting the 'sepsis syndrome'. The clinical characteristics of this condition include fever, hypotension, hypoglycaemia, disseminated intravascular coagulation and increased vascular permeability. Recent evidence suggests that the cytokines tumour necrosis factor (TNF) and interleukin (IL) types 1 and 6 play a pivotal role in mediating this aberrant host response to major trauma and infection.

Although cytokines are a diverse group of proteins, they share a number of characteristic properties (*Table 1*). They can be loosely divided into three groups: (1) the monokines (e.g. TNF-α, IL-1), which are produced predominantly by mononuclear phagocytes; (2) the lymphokines (e.g. IL-2, interferon (IFN) γ), which are produced mainly by lymphocytes; and (3) the colony-stimulating factors (e.g. granulocyte–macrophage colony-stimulating factor; GM-CSF), which are produced by both lymphocytes and mononuclear phagocytes. This paper examines the function of the inflammatory cytokines TNF-α, IL-1 and IL-6, which are produced predominantly by mononuclear phagocytes in response to tissue injury and infection, and reviews recent developments that attempt to limit the consequences of excessive release in these conditions.

Tumour necrosis factor (cachectin)

This cytokine received its dual title following the independent discovery of its ability to cause cachexia and hypertri-

Table 1 *Characteristic features of all cytokines*

Protein hormones active at very low concentrations ($<10^{-11}$ mol/l)
Produced during the effector stages of natural and specific immunity
Like other polypeptide hormones, they initiate action by binding to specific receptors on the surface of target cells, where cell division is often regulated (i.e. function as growth factors)
Produced by a diverse range of cells, at multiple sites and often have overlapping actions
Act on a wide range of different cells and often influence the synthesis of other cytokines
Serve to mediate and regulate immune and inflammatory responses and have important autocrine, paracrine and endocrine actions
Invoke mostly slow cellular responses involving new protein synthesis

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* *Mononuclear phagocyte refers to all cells of the mononuclear phagocyte lineage, including monocytes, Kupffer cells and peritoneal, pulmonary and other macrophages*

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glyceridaemia in experimental animals[1,2], and necrosis of transplantable tumours[3]. Although the term 'tumour necrosis factor' was originally coined by Carswell *et al.*[3] in 1975, it is likely that the New York surgeon William Coley described the same agent in 1893. He reported the presence of a toxin in inoculations of erysipelas that induced necrosis of malignant tumours[4]. Subsequent experiments revealed that the bacterial cell wall product lipopolysaccharide (LPS) induced a haemorrhagic necrosis of subcutaneous tumours[5,6] by stimulating the release of the endogenous mediator TNF.

TNF is a 157 amino acid polypeptide, derived from a 233 amino acid prohormone through a series of proteolytic cleavages[7]. The cytokine interacts with a specific receptor that is present on a wide variety of cells[8–10], and can achieve a biological response with as little as 5 per cent occupancy of its receptors[10]. It mediates many of its diverse effects through cell–cell interactions (paracrine function) via a bioactive cell-associated intermediate species[11]. Although produced by many different cell types, the major cellular source of TNF is the activated mononuclear phagocyte[12–14].

The chief physiological stimulus for the release of TNF is LPS (endotoxin)[15]. Other stimuli include bacterial exotoxins, viruses, protozoans and fungi[16,17]. Intravenous administration of LPS to volunteers[18,19] is followed by an early monophasic rise in serum TNF levels. Peak levels occur after 90–120 min and return to baseline within 6 h. The local concentration of TNF may, however, be several times higher in regional infections[20]. Any brief exposure to TNF induces a cascade of secondary reactions that continue to have an effect long after its disappearance from the serum. It is likely that many of these secondary actions are related to the release of IL-1, with which TNF has many synergistic actions[21–24].

Functions of tumour necrosis factor

Leucocytes and mononuclear phagocytes

From a teleological perspective, TNF may be seen as an inflammatory cytokine that acts rapidly to induce an appropriate response to tissue injury and infection. In keeping with this concept, it induces a leucocytosis and stimulates enhanced activation, margination and transendothelial migration of neutrophils[25–28], leading to improved antibody-dependent cellular cytotoxicity and neutrophil-mediated inhibition of fungal growth[29]. It also enhances the maturation and activation of monocytes and macrophages[30,31], thus further stimulating its own release[32] and promoting the inhibition of intracellular replication of viruses and parasites[33].

Metabolic function

TNF plays a vital role in mobilizing body stores of energy that are necessary to fight infection and fuel healing in the patient with trauma. Although TNF has wide-ranging actions on protein and fat metabolism, when viewed together its overall effect is to stimulate a redistribution of proteins and fats from the periphery to the liver during injury[34]. It promotes the release of amino acids from peripheral proteins[35] and causes degradation of skeletal muscle[36]. Chronic administration therefore leads to significant peripheral wasting[34,37]. In addition, TNF stimulates the release of triglycerides from adipose tissue[1,2,38] and inhibits synthesis of fatty acids[7,39]. It also induces anaerobic glycolysis by increasing cellular transport of glucose, depletion of glycogen and increased efflux of lactate[40]. These actions suggest that it may play a role in the rapid development of lactic acidosis following septic shock. Despite its catabolic actions on peripheral protein and fat metabolism, TNF has selective anabolic effects in the liver, where it stimulates hepatic uptake of amino acids and hepatic lipogenesis, fuelling increased synthesis of acute-phase proteins but preserving hepatic mass despite peripheral wasting[34,35,41,42].

Central effects

TNF acts as an endogenous pyrogen by stimulating hypothalamic synthesis of prostaglandins[43]. The fever produced is biphasic, with the second peak caused by TNF-induced release of IL-1. Induction of a fever may be seen as an immunoenhancing action in the mobilization of host defence mechanisms[44].

Coagulation and wound healing

TNF also displays a marked procoagulant action on endothelial surfaces, leading to microthrombosis, which appears to be the basis for its antitumour action[45–47]. Intravenous infusion of TNF in human volunteers induces a rapid and sustained activation of the common pathway of the coagulation system, probably through activation of the extrinsic route[48]. It also induces fibroblast proliferation[49], microvascular proliferation[50] and stimulates the release of collagenase[51], actions that are essential for the organization and maturation of healing wounds.

Tumour necrosis factor in disease states

The importance of TNF in mobilizing the acute inflammatory response is reflected in studies that have reported increased mononuclear phagocyte production following major traumatic, surgical and thermal injury[52–54]. In addition, several studies have reported that 40–80 per cent of patients with sepsis have detectable levels of immunoreactive serum TNF[55–57]. Increased synthesis of this cytokine thus appears to represent a common pathway in the host response to severe tissue injury and infection. Rather than indicating an effective host response, however, increased production in these conditions is commonly associated with a poor prognosis[54–58].

Interleukin 1

IL-1 was known by a number of names until amino acid sequencing revealed a closely related family of polypeptide hormones to be responsible for all these actions (*Table 2*). Whereas IL-1α and IL-1β are the product of two separate genes and display only 30 per cent amino acid identity, they bind with equal affinity to the same receptor[59]. IL-1α is synthesized initially as a high molecular weight (33-kDa) bioactive precursor. This is degraded to a 17-kDa membrane form[60] that can modulate local cell function[61] even in the absence of soluble IL-1. The majority of synthesized IL-1 is retained intracellularly as only 20 per cent is degraded and released in its active 17-kDa form[62]. Non-specific proteases that effect this change are present in high concentrations in blood clots as well as in traumatized and infected tissues.

The activated mononuclear phagocyte is the major source of IL-1, although endothelial cells, keratinocytes, neutrophils and B lymphocytes are also capable of producing this cytokine[63]. Although LPS is the major physiological stimulus, other agents including silica, TNF and IL-1 itself can also induce its synthesis[64,65]. IL-1α has not been detected in serum and IL-1β only inconsistently in the serum of patients with sepsis, further supporting the evidence that suggests that this cytokine mediates many of its actions through a membrane-bound form. LPS infusion in volunteers is occasionally followed by an IL-1β peak at 180 min, although this is consistently detected after induction of a lethal Gram-negative septicaemia in primates[19,66].

Table 2 *Names of factors by which interleukin 1 was known before amino acid sequencing revealed them to be identical*

Lymphocyte-activating factor
Endogenous or leucocytic pyrogen
Leucocyte endogenous mediator
Osteoclast-activating factor
B cell-stimulatory factor
Catabolin
Haemopoietin 1
Proteolysis-inducing factor

Functions of interleukin 1

Immunity

In comparison with TNF, IL-1 has more global inflammatory and immunoenhancing functions. Its actions include powerful costimulation of T cells resulting in T cell blastogenesis, enhanced IL-2 synthesis and expression of IL-2 receptors[67,68]. It also augments production of IFN-α and cytotoxic T lymphocytes[69].

Myelopoiesis and leucocyte function

IL-1 has potent actions on myelopoiesis, both directly and by inducing production of several myelopoietic growth factors, including GM-CSF[70]. Stimulation of marrow precursors also accounts for its ability to protect against lethal infection in normal and neutropenic animals[71,72]. Local release of IL-1 stimulates an influx of granulocytes into sites of acute inflammation[21,47] by increasing margination and migration of activated leucocytes into inflammatory loci[73]. It also acts locally to stimulate the proliferation of fibroblasts and vascular smooth muscle cells[74,75]. Although these actions are beneficial in the localization of infection, excessive IL-1- and TNF-mediated margination of activated neutrophils may lead to pulmonary inflammation and congestion[76].

Central and endocrine function

As with TNF, IL-1 is an endogenous pyrogen, raising temperature by inducing release of prostaglandins in the anterior hypothalamus[77]. It has several other central actions including the development of anorexia[78] and increases the frequency and duration of slow-wave sleep comparable to the changes seen during illness[79]. IL-1 acts on the neuroendocrine axis, stimulating the release of adrenocorticotrophic hormone, thyroid-stimulating hormone and somatostatin[80–82]. It directly stimulates the release of adrenal corticosteroids[83] and pancreatic release of insulin and glucagon[84].

Synergism with tumour necrosis factor

TNF and IL-1 display many similar actions and not only stimulate their own release, but also the release of each other, thus amplifying the cascade of inflammatory mediators after injury[32,43,85,86]. It is not, therefore, surprising that these cytokines display synergistic actions on cells from many tissues, including the pituitary gland, bone, endothelium, pancreas and skin fibroblasts[63]. IL-1 and TNF also display similar actions on neutrophil adherence and activation[25,87], and inflammatory reactions[47]. They both stimulate the release of hepatic acute-phase proteins, although TNF has more potent actions on peripheral amino acid and fat metabolism[34,35,42,88]. Combined infusion of TNF and IL-1 produces haemodynamic instability and metabolic effects at concentrations that have only minimal effects when infused separately[23,24,89]. As with TNF, IL-1 also promotes the development of disseminated intravascular coagulation, although by a different action, as it reduces heparin sulphate binding[45,90].

Interleukin 1 in disease states

IL-1 has also been detected in the serum of children with septic purpura[91], Kawasaki's syndrome[92] and rheumatoid arthritis[93], and is found in the synovial fluid of inflamed joints[94]. Along with TNF, IL-1 has been implicated in the pathogenesis of cancer cachexia[95], although it is likely that weight loss in malignant disease is secondary to a combination of factors. Production of IL-1 is significantly increased following surgical trauma, thermal injury and haemorrhagic shock[96–99]. This cytokine is also detected in the serum of patients with severe sepsis[19,56].

Interleukin 6

In common with both TNF and IL-1, IL-6 was isolated independently for a number of different biological properties, including IFN-β_2, hepatocyte-stimulating factor and B cell differentiation factor BSF-2[100,101]. It is secreted by fibroblasts, monocytes and macrophages, as a range of differentially modified phosphoglycoproteins[102]. *In vitro* synthesis is stimulated by a number of cytokines including TNF, IL-1 and platelet-derived growth factor, and in response to viral and bacterial infection[103]. It is rapidly released into the circulation in response to injury and is detected in the circulation of volunteers within 1 h of injection of LPS[104]. As with all other cytokines, IL-6 exerts its effects by binding to a specific receptor, which has recently been cloned[105].

Functions

In vitro studies using this family of glycoproteins have revealed a range of actions that often overlap and are complementary to those of TNF and IL-1. IL-6 enhances immune function by inducing an antiviral state in fibroblasts, stimulates differentiation of lymphocytes and induces proliferation and antibody production in B cells[106,107]. In common with both IL-1 and TNF, IL-6 induces the synthesis and release of a number of hepatic acute-phase proteins including C-reactive protein, serum amyloid A, fibrinogen and α_1-antitrypsin[108], and plays an important part in the reprioritization of synthesis of hepatic proteins after many forms of tissue injury and infection[109]. IL-6 is released into the systemic circulation following tissue trauma and infection, where levels appear to correlate with subsequent death[109–111].

Cytokines and the sepsis syndrome

Despite the introduction of broad-spectrum antibiotics, infection remains an important cause of hospital morbidity, where five of every 1000 admissions are complicated by bacterial sepsis leading to shock. Sepsis is one of the most important causes of multiple system organ failure, which accounts for 70 000 deaths in the USA each year[112]. Infection is also an important cause of mortality in the severely traumatized patient and is responsible for 50–70 per cent of all burn-related deaths[113,114].

Tumour necrosis factor

It has long been recognized that many of the deleterious consequences of Gram-negative sepsis are caused by bacterial endotoxin (LPS). Recent evidence suggests that LPS mediates its toxic effects through stimulation of cells of the mononuclear phagocyte lineage[115,116]. Of the dozens of mediators released by these cells, TNF, IL-1 and to a lesser extent IL-6 appear to play a pivotal role in mediating the acute effects of Gram-negative sepsis and shock. Beutler *et al.* initially reported that endotoxin-resistant C3H/HeJ mice did not produce TNF in response to bacterial challenge[15]. Further studies confirmed the importance of this cytokine in mediating the immediate clinical consequences of LPS challenge[13]. Subsequent studies revealed that infusion of high concentrations of TNF in rats produced lactic acidosis, hypotension and death. Post-mortem examination of these animals revealed adrenal necrosis, pulmonary congestion, caecal necrosis, intestinal ischaemia, pancreatic infarction, pulmonary inflammation and anuria[117,118]. Similar findings were reported in dogs, which also displayed a reduction in cardiovascular output and hypotension before death[119]. Administration of TNF was also associated with a rise in counter-regulatory hormones (including glucagon, cortisol and adrenaline), lactate, depression of the resting membrane potential in muscle and sequestration of fluid. In these animals, the changes were indistinguishable from those induced by direct infusion of LPS[119,120]. Further work revealed that passive immunization with both polyclonal and monoclonal antibodies directed against the TNF molecule protected against the lethal effects of LPS infusion in murine and primate models of septic shock[121,122].

This experimental evidence, which strongly suggests a critical role for TNF in the pathogenesis of the sepsis syndrome, was subsequently confirmed in several clinical studies that revealed a high positive correlation between serum levels of TNF and both severity of illness and mortality in septic shock[19,56,57]. Calandra *et al.* reported a progressive decline in TNF levels in survivors of septic shock, whereas TNF levels remained persistently raised after initial diagnosis and treatment in non-survivors[56]. Marks *et al.*[55] also reported a close correlation between the detection of TNF in the serum of patients suffering from shock (septic and non-septic) and the risk of developing adult respiratory distress syndrome (55 *versus* 26 per cent), or subsequent mortality (81 *versus* 43 per cent), while Offner *et al.* reported a significant correlation between the APACHE II score and TNF levels in patients with sepsis[57]. Although increased synthesis of TNF may simply reflect the severity of the injury or infection, Takayama *et al.* noted significantly increased synthesis of this cytokine for up to 3 days before the onset of clinical infection[53], suggesting a causative role in the evolution of septic episodes. These data further reinforce experimental evidence which suggests that, rather than improving the host immune response, excessive production of TNF predisposes to the development of sepsis and in combination with other mediators is responsible for the clinical syndrome of septic shock.

Interleukin 1

As with TNF, IL-1 has also been implicated as an important mediator of septic shock. Although infusion of IL-1 alone induces leucopenia, tachycardia and hypotension, the cytokine acts synergistically with TNF to produce tissue damage and death in experimental models[23,24]. In contrast to the proven prognostic value of raised serum TNF levels in patients with sepsis, the detection of serum IL-1 appears to be of variable significance. Serum IL-1 concentration is commonly raised in non-survivors of septic shock, although the difference does not persist beyond the first day after diagnosis and treatment[56]. Cannon *et al.* also reported raised serum IL-1 levels in patients with sepsis compared with healthy controls[19] and Waage *et al.* noted that the presence of IL-1 in the serum of patients with sepsis was associated with a poorer prognosis[58]. Luger *et al.*, however, found that patients with fatal sepsis had significantly lower serum IL-1 activity[123].

Interleukin 6

Experimental LPS infusion in human volunteers and lethal Gram-negative septicaemia in primates also induce the release of IL-6 into the circulation[66,124,125]. IL-6 levels correlate positively with mortality rates in patients with sepsis[56,111] and recent experimental evidence implicates this cytokine as an important comediator in lethal *Escherichia coli* infection[126].

Immunomodulation

As previously outlined, a large body of evidence suggests that the bacterial cell wall product LPS (endotoxin) induces the clinical syndrome of septic shock by stimulating the mononuclear phagocyte to release a range of cellular products. In this regard, excessive release of TNF, IL-1 and possibly IL-6 appears to play a pivotal role in mediating this aberrant host response to Gram-negative infection. Attempts to modulate this detrimental response have led to the development of therapies designed either to neutralize endotoxin directly, to inhibit cytokine release from cells or to protect against the consequences of excessive cytokine release by directly blocking the action of these endogenous mediators (*Figure 1*).

Lipopolysaccharide

Several studies have attempted to reduce endotoxaemia using polymyxin B, a polysaccharide antibiotic that also has a significant antiendotoxin effect. This drug improves survival in experimental animal models of burn sepsis[127] and in clinical trials has been shown to reduce significantly endotoxaemia after thermal injury[128]. Although the results of these early studies are encouraging, the potential toxicity of the antibiotic after parenteral administration may limit its clinical potential.

More intensive study has focused on the development of antibodies designed to block the active portion of the LPS molecule. Endotoxin consists of three distinct antigenic regions: the polysaccharide side chain (O), the core (R) and a lipid moiety (A). The O antigen varies between organisms and has not therefore proved useful in the development of an antigen active against different Gram-negative pathogens.

One of the earliest clinical reports on the use of antiendotoxin antibodies was published by Ziegler *et al.*[129] in 1982. Using a polyclonal human antibody raised against the R and O antigens of a mutant strain of *E. coli* (J5), they reported a reduction in mortality rate (39 *versus* 22 per cent) in a controlled clinical trial of patients with Gram-negative bacteraemia from focal Gram-negative infection. The antibody also significantly reduced death from Gram-negative sepsis when used

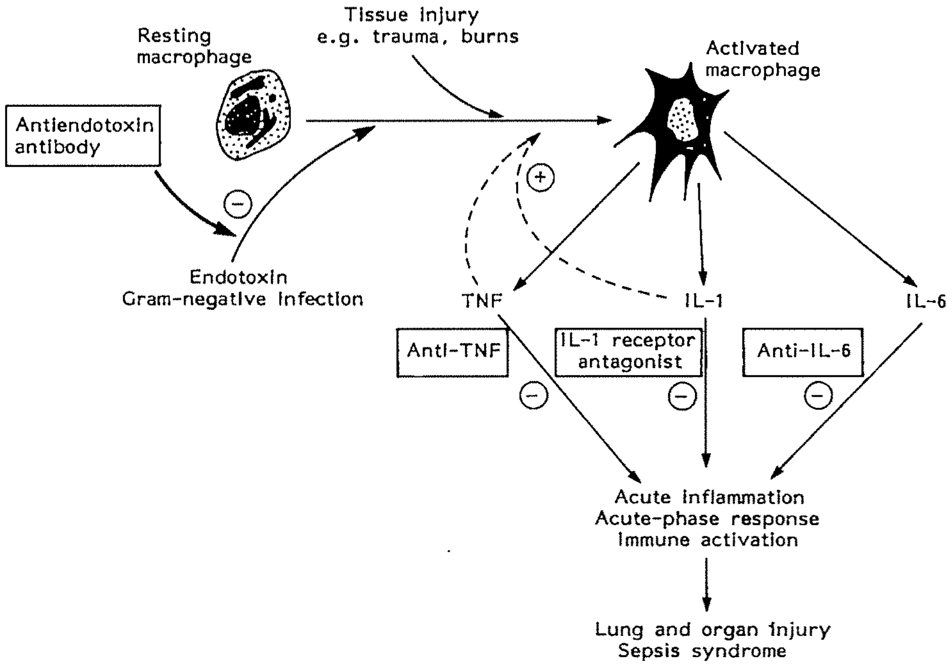

Figure 1 *Diagrammatic representation of therapeutic strategies designed to downregulate macrophage activation. TNF, tumour necrosis factor; IL, interleukin*

prophylactically in high-risk patients[130]. Its widespread use was not, however, feasible because of the need for repeated inoculation of human donors and the risk of disease transmission to recipients. More recently, monoclonal immunoglobulin M (IgM) antibodies directed against the lipid A moiety (HA-1A) have become commercially available. In a large multicentre clinical trial, the HA-1A antibody significantly reduced deaths in patients with Gram-negative bacteraemia (49 *versus* 30 per cent) and in those with Gram-negative shock (57 *versus* 33 per cent)[131]. Although these results appear encouraging, it must be borne in mind that it is not usually possible to define which patient population will have positive Gram-negative blood cultures at the time of administration of the antibody (this was the only group to benefit from therapy). Treatment did not have any deleterious or beneficial effect when given to patients with shock or sepsis who did not have Gram-negative bacteraemia. If given to all patients with sepsis at presentation without waiting for the results of blood culture, survival would be expected to increase only from 39 to 43 per cent[131]. In a second trial using a murine IgM antibody directed against the lipid A moiety of the J5 mutant *E. coli* strain, Greenman *et al.* reported a significant reduction in deaths (30 *versus* 43 per cent) when the E5 antibody was used in non-shocked patients with Gram-negative septicaemia[132]. In contrast to the HA-1A antibody, it did not significantly improve survival in patients suffering from Gram-negative shock. Overall the antibody did not significantly improve survival compared with controls, even though the trial was confined to those in whom Gram-negative sepsis was suspected. It therefore appears that antiendotoxin therapy is indicated in patients only when there is a strong clinical suspicion of Gram-negative septicaemia. Approximately 30 per cent of patients treated under these criteria will still turn out not to have positive blood cultures for a Gram-negative organism. The efficacy of delaying therapy until the results of blood culture become available is not known, although experimental evidence suggests that early intervention is required if therapy is to have its desired effect.

Tumour necrosis factor and interleukins 1 and 6

Although the results of clinical trials using antiendotoxin therapy are encouraging, these antibodies are limited in their usefulness to patients with Gram-negative sepsis. Recent work has focused on the development of regimens designed to downregulate the host response to excessive TNF, IL-1 and IL-6 release that commonly occurs after major thermal and traumatic injury, and during infection caused by organisms other than Gram-negative bacteria.

These cytokines may be blocked by pretreatment with specific neutralizing antibodies. Initial studies using anti-TNF antibodies suggested that they protect mice and rabbits against the lethal effects of both LPS and live Gram-negative bacteria[122,123]. Further studies using primate models of septic shock have confirmed the ability of monoclonal anti-TNF antibody to improve survival not only when given before, but also up to 30 min after commencing a lethal infusion of Gram-negative bacteria[121,133,134]. These neutralizing antibodies also protect against the metabolic consequences of septic shock and prevent the release of IL-1 and IL-6 in primate models of bacteraemia[121,125]. To date, there are no reports on the use of anti-TNF therapy in controlled clinical trials, although a small phase I clinical trial using murine anti-TNF antibodies in severe sepsis noted that treatment conferred a beneficial effect on haemodynamic stability[135]. The results of ongoing large-scale clinical trials are awaited.

Other agents that specifically inhibit TNF release from the mononuclear phagocyte population include the xanthine derivative pentoxifylline. Pretreatment with this drug has been shown to improve survival in murine models of endotoxic shock[136], although it is unclear whether it will have a useful role in clinical practice.

Although much attention has focused on the role of TNF in mediating the deleterious effects of septic shock, recent evidence suggests that this cytokine may act in part by stimulating the release of IL-1, with which it synergizes to increase the haemodynamic instability and lethality of LPS infusion[23,24]. As a consequence, investigators have developed antibodies designed to block the action of IL-1. This has been achieved using the IL-1 receptor antagonist molecule. This naturally occurring protein has a remarkably similar amino acid sequence to both IL-1α and IL-1β[137]. Although it binds selectively to the IL-1 receptor, it displays no agonist action and is capable of blocking IL-1 *in vitro* and *in vivo*[138]. It is produced in increased quantities in septic and inflammatory conditions and appears to limit the severity of these by antagonizing the action of endogenous IL-1. A recombinant human IL-1 receptor antagonist has been synthesized and blocks the hypotension and leucopenia that follow intravenous injection of IL-1β. The receptor antagonist dramatically reduces the lethality of LPS and staphylococcal-induced shock in experimental animals, even when given up to 2 h after LPS infusion[139,140]. Preliminary results[141] from a small clinical trial using the IL-1 receptor antagonist in sepsis suggest that it improves survival in a dose-dependent fashion, reducing the mortality rate from 44 per cent in a placebo group to 16 per cent in a group that received a dose of 133 mg/h for 72 h. The results of larger clinical trials are eagerly awaited.

In contrast to TNF and IL-1, which appear to act singly and synergistically to effect hypotension and death, IL-6 does not produce tissue damage or haemodynamic instability when administered *in vivo*. Despite this apparent lack of toxicity, at least one study has reported that anti-IL-6 monoclonal antibodies protect against lethal *E. coli* infection and lethal TNF challenge in mice[126], suggesting that it too acts as a comediator in Gram-negative sepsis. It is not, however, clear whether anti-IL-6 therapy will have a role in clinical practice.

Potential pitfalls of therapy

Although many of these therapeutic regimens have shown impressive results in experimental trials, the benefits of therapy must be weighed against the potential side-effects. In many of the experimental animal studies that have reported on the beneficial effects of antiendotoxin, anti-TNF and IL-1 receptor antagonist therapy, treatment was instituted immediately before or, at most, within 2 h of challenge with a single dose of LPS. In these studies the timing of therapy was critical; it did not appear to be of benefit if given after the full syndrome of septic shock had developed. The clinical syndrome of septic shock is rarely the result of release of a single massive dose of bacterial endotoxin. Patients with sepsis more commonly have a continuing focus of infection from which endotoxin and bacteria are released intermittently. Concerns over the therapeutic efficacy of antiendotoxin and IL-1 receptor antagonist antibodies in these patients have not however materialized, as clinical trials have shown therapy to be of benefit even after the onset of septic shock[131,133,141]. In particular, antiendotoxin therapy in these patients is likely to act by protecting against the effect of subsequent episodes of endotoxaemia and bacteraemia, rather than directly influencing the condition of the patient at the time of administration of the antibody.

In contrast, the clinical role of anti-TNF therapy in the presence of a continuing septic focus remains unclear. TNF production during infection mobilizes immune function by increasing IL-1 production, inducing leucocytosis and fever, and by stimulating enhanced elimination of pathogens[25–33]. Pretreatment with TNF improves survival in models of regional or slowly developing sepsis such as peritonitis[142]. This cytokine therefore appears to be necessary for the early localization of regional infections. The value of anti-TNF therapy in persisting or indolent infections that more closely resemble septic states in clinical practice has not been fully assessed. Concerns over anti-TNF therapy have been realized in at least one study, which reported a higher mortality rate following the administration of anti-TNF antibodies in an experimental model of bacterial peritonitis[143].

Conclusions

Activation of mononuclear phagocyte cells, with concomitant release of a range of inflammatory mediators, is an integral part of the host response to trauma and infection. Of these mediators, the cytokines TNF, IL-1 and IL-6 play a pivotal role in initiating the host response by helping to induce an acute inflammatory response, stimulating immune function and initiating processes necessary for tissue repair and regeneration. Major trauma and sepsis may, however, lead to widespread overproduction of these cytokines and at detectable serum concentrations they have many deleterious actions on metabolic function and haemodynamic stability. New therapies designed to downregulate their synthesis in response to LPS, or to modify the host response to soluble cytokines through the use of blocking antibodies or receptor antagonists, hold much promise for the treatment of patients with trauma or sepsis. It is becoming increasingly apparent, however, that no single agent is responsible for all the clinical and metabolic manifestations of the sepsis syndrome. As efforts to regulate this aberrant host response become more refined, the efficacy of combined therapy is likely to become apparent. Careful evaluation of the benefits and possible complications of these therapies will be required before advocating their use outside controlled clinical trials.

References

1. Rouzer CA, Cerami A. Hypertriglyceridemia associated with *Trypanosoma brucei* infection in rabbits: role of defective triglyceride removal. *Mol Biochem Parasitol* 1980; **2**: 31–8.
2. Guy MW. Serum and tissue fluid lipids in rabbits experimentally infected with *Trypanosoma brucei. Trans R Soc Trop Med Hyg* 1975; **69**: 429A.
3. Carswell EA, Old LJ, Kassel RL *et al.* An endotoxin-induced serum factor that causes necrosis of tumors. *Proc Natl Acad Sci U S A* 1975; **72**: 3666–70.
4. Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas, with a report of ten original cases. *Am J Med Sci* 1893; **105**: 487–511.
5. Hartwell JL, Shear MJ, Adams JR Jr. Chemical treatment of tumors – VII. Nature of the hemorrhage producing fraction from *Serratia marcescens* (*Bacillus progidiosus*) culture filtrate. *J Natl Cancer Inst* 1943; **4**: 107–22.
6. O'Malley WE, Achinstein B, Shear MJ. Action of bacterial polysaccharide on tumors – II. Damage of sarcoma 37 by serum of mice treated with *Serratia marcescens* polysaccharide, and induced tolerance. *J Natl Cancer Inst* 1962; **29**: 1169–75.
7. Beutler B, Mahoney J, Le Trang N *et al.* Purification of cachectin, a lipoprotein lipase-suppressing hormone secreted by endotoxin-induced RAW 264.7 cells. *J Exp Med* 1985; **161**: 984–95.
8. Aggarwal BB, Eessalu TE, Haas PE. Characterization of the receptors for human tumour necrosis factor and their regulation by γ interferon. *Nature* 1985; **318**: 665–7.
9. Baglioni C, McCandless S, Tavernier J *et al.* Binding of human tumor necrosis factor to high affinity receptors on HeLa and lymphoblastoid cells sensitive to growth inhibition. *J Biol Chem* 1985; **260**: 13 395–7.
10. Tsujimoto M, Vilcek J. Tumor necrosis factor receptors in HeLa cells and their regulation by interferon gamma. *J Biol Chem* 1986; **261**: 5384–8.
11. Kriegler M, Perez C, DeFay KA *et al.* A novel form of TNF/cachectin is a cell surface cytotoxic transmembrane protein: ramifications for the complex physiology of TNF. *Cell* 1988; **53**: 45–53.
12. Hesse DG, Davatelis G, Felsen D *et al.* Cachectin/tumor necrosis factor gene expression in Kupffer cells. *J Leukoc Biol* 1987; **42**: 422–31.
13. Beutler B, Cerami A. Cachectin: more than a tumor necrosis factor. *N Engl J Med* 1987; **316**: 379–85.
14. Matthews N. Tumor necrosis factor from the rabbit – V. Synthesis *in vitro* by mononuclear phagocytes from various tissues of normal and BCG-infected rabbits. *Br J Cancer* 1981; **44**: 418–24.
15. Beutler B, Krochin N, Milsark IW *et al.* Control of cachectin (tumor necrosis factor) synthesis: mechanism of endotoxin resistance. *Science* 1986; **232**: 977–80.
16. Wong GHW, Goeddal DV. Tumor necrosis factor alpha and beta inhibit virus replication and synergize with interferons. *Nature* 1986; **23**: 819–21.
17. Hotez PJ, Le Trang N, Fairlamb AH *et al.* Lipoprotein lipase suppression in 3T3-L1 cells by hematoprotozoan induced mediator from peritoneal exudate cells. *Parasite Immunol* 1984; **6**: 203–9.
18. Blick M, Sherwin SA, Rosenblum M *et al.* Phase I study of recombinant tumor necrosis factor in cancer patients. *Cancer Res* 1987; **47**: 2986–9.
19. Cannon JG, Tompkins RG, Gelfand JA *et al.* Circulating interleukin-1 and tumor necrosis factor in septic shock and experimental endotoxin fever. *J Infect Dis* 1990; **161**: 79–84.
20. Leist TP, Frei K, Kam-Hansen S *et al.* Tumor necrosis factor alpha in cerebrospinal fluid during bacterial but not viral meningitis. *J Exp Med* 1988; **167**: 1743–8.
21. Cybulsky MI, Colditz IG, Movat HZ. The role of interleukin 1 in neutrophil leukocyte emigration induced by endotoxin. *Am J Pathol* 1986; **124**: 367–72.
22. White CW, Ghezzi P, Dinarello CA *et al.* Recombinant tumor necrosis factor/cachectin and interleukin-1 pretreatment decreases lung oxidized glutathione accumulation, lung injury, and mortality in rats exposed to hyperoxia. *J Clin Invest* 1987; **79**: 1868–73.
23. Okusawa S, Gelfand JA, Ikejima T *et al.* Interleukin 1 induces a shock-like state in rabbits. Synergism with tumor necrosis factor and the effect of cyclooxygenase inhibition. *J Clin Invest* 1988; **81**: 1162–72.
24. Everaerdt B, Brouckaert P, Shaw A, Fiers W. Four different interleukin-1 species sensitize to the lethal action of tumour necrosis factor. *Biochem Biophys Res Commun* 1989; **163**: 378–85.
25. Gamble JR, Harlan JM, Klebanoff SJ *et al.* Stimulation of the adherence of neutrophils to umbilical vein endothelium by recombinant human tumor necrosis factor. *Proc Natl Acad Sci U S A* 1985; **82**: 8667–71.
26. Shalaby MR, Aggarwal BB, Rinderknecht E *et al.* Activation of human polymorphonuclear neutrophils functions by interferon γ and tumor necrosis factor. *J Immunol* 1985; **135**: 2069–73.
27. Moser R, Schleiffenbaum B, Groscurth P, Fehr J. Interleukin-1 and tumor necrosis factor stimulate human vascular endothelial cells to promote transendothelial neutrophil passage. *J Clin Invest* 1989; **83**: 444–55.
28. Ulich TR, del Castillo J, Keys M *et al.* Kinetics and mechanisms of recombinant human interleukin 1 and tumor necrosis factor-α-induced changes in circulating numbers of neutrophils and lymphocytes. *J Immunol* 1987; **139**: 3406–15.
29. Djeu JY, Blanchard DK, Halkias D *et al.* Growth inhibition of *Candida albicans* by human polymorphonuclear neutrophils: activation by interferon-γ and tumor necrosis factor. *J Immunol* 1986; **137**: 2980–4.
30. Philip R, Epstein LB. Tumor necrosis factor as immunomodulator and mediator of monocyte cytotoxicity induced by itself, interferon gamma and interleukin-1. *Nature* 1986; **323**: 86–9.
31. Munker R, Gasson J, Ogawa M *et al.* Recombinant human TNF induces production of granulocyte–macrophage colony stimulating factor. *Nature* 1986; **323**: 79–82.
32. Le J, Vilček J. Tumor necrosis factor and interleukin-1: cytokines with multiple overlapping biological activities. *Lab Invest* 1987; **56**: 234–48.
33. Mestan J, Digel W, Mittnacht S *et al.* Antiviral effects of recombinant tumor necrosis factor *in vitro. Nature* 1986; **323**: 816–19.
34. Fong Y, Moldawer LL, Marano M *et al.* Cachectin/TNF or IL-1 alpha induces cachexia with redistribution of body proteins. *Am J Physiol* 1989; **256**: R659–65.
35. Warren RS, Donner DB, Starnes HF Jr, Brennan MF. Modulation of endogenous hormone action by recombinant human tumor necrosis factor. *Proc Natl Acad Sci U S A* 1987; **84**: 8619–22.
36. Flores EA, Bistrian BR, Pomposelli JJ *et al.* Infusion of tumor necrosis factor/cachectin promotes muscle catabolism in the rat. A synergistic effect with interleukin 1. *J Clin Invest* 1989; **83**: 1614–22.

37. Tracey KJ, Wei H, Manogue KR *et al.* Cachectin/TNF induces cachexia, anemia and inflammation. *J Exp Med* 1988; **167**: 1211–27.
38. Zechner R, Newman TC, Sherry B *et al.* Recombinant human cachectin/tumor necrosis factor but not interleukin 1 down-regulates lipoprotein lipase gene expression at the transcriptional level in mouse 3T3-L1 adipocytes. *Mol Cell Biol* 1988; **8**: 2394–401.
39. Patton JS, Shepard HM, Wilking H *et al.* Interferons and tumor necrosis factors have similar catabolic effects on 3T3-L1 cells. *Proc Natl Acad Sci U S A* 1986; **83**: 8313–17.
40. Lee MD, Zentella A, Pekala PH, Cerami A. Effect of endotoxin induced monokines on glucose metabolism in the muscle cell line L-6. *Proc Natl Acad Sci U S A* 1987; **84**: 2590–4.
41. Feingold KR, Grunfeld C. Tumor necrosis factor-alpha stimulates hepatic lipogenesis in the rat *in vivo*. *J Clin Invest* 1987; **80**: 184–90.
42. Moldawer LL, Andersson C, Gelin J *et al.* Regulation of food intake and hepatic protein synthesis by recombinant derived monokines. *Am J Physiol* 1987; **254**: G450–6.
43. Dinarello CA, Cannon JG, Wolff SM *et al.* Tumor necrosis factor (cachectin) is an endogenous pyrogen and induces production of interleukin-1. *J Exp Med* 1986; **163**: 1433–50.
44. Jampel HD, Duff GW, Gershon RK *et al.* Fever immunoregulation – III. Hyperthermia augments the primary *in vitro* humoral immune response. *J Exp Med* 1983; **157**: 1229–38.
45. Bevilacqua MP, Pober JS, Majeau GR *et al.* Recombinant tumor necrosis factor induces procoagulant activity in cultured human vascular endothelium: characterization and comparison with the actions of interleukin 1. *Proc Natl Acad Sci U S A* 1986; **83**: 4533–7.
46. Manda T, Shimomura K, Mokumoto S *et al.* Recombinant human tumor necrosis factor α; evidence of an indirect mode of antitumor activity. *Cancer Res* 1987; **47**: 1307–11.
47. Cybulsky MI, Chan MKW, Movat H *et al.* Acute inflammation and microthrombosis induced by endotoxin, interleukin-1, and tumor necrosis factor and their implication in Gram negative infection. *Lab Invest* 1988; **58**: 365–78.
48. Van Der Poll T, Büller HR, Ten Cate H *et al.* Activation of coagulation after administration of tumor necrosis factor to normal subjects. *N Engl J Med* 1990; **322**: 1622–7.
49. Sugarman BJ, Aggarwal BB, Hass PE *et al.* Recombinant tumor necrosis factor α: effects on proliferation of normal and transformed cells *in vitro*. *Science* 1985; **230**: 943–5.
50. Fràter-Schröder M, Risau W, Hallmann R *et al.* Tumor necrosis factor type alpha, a potent inhibitor of endothelial cell growth *in vitro*, is angiogenic *in vivo*. *Proc Natl Acad Sci U S A* 1987; **84**: 5277–81.
51. Dayer JM, DeRochemonteix B, Burrus B *et al.* Human recombinant interleukin 1 stimulates collagenase and prostaglandin E_2 production by human synovial cells. *J Clin Invest* 1986; **77**: 645–8.
52. Pullicino EA, Carli F, Poole S *et al.* The relationship between the circulating concentrations of interleukin 6 (IL-6), tumor necrosis factor (TNF) and the acute phase response to elective surgery and accidental injury. *Lymphokine Res* 1990; **9**: 231–8.
53. Takayama TK, Miller CL, Szabo G. Elevated tumor necrosis factor alpha production concomitant to elevated prostaglandin E_2 production by trauma patients' monocytes. *Arch Surg* 1990; **125**: 29–35.
54. Marano MA, Fong Y, Moldawer LL *et al.* Serum cachectin/TNF in critically ill burn patients correlates with infection and mortality. *Surg Gynecol Obstet* 1990; **170**: 32–8.
55. Marks JD, Marks CB, Luce JM *et al.* Plasma tumor necrosis factor in patients with septic shock: mortality rate, incidence of adult respiratory distress syndrome, and effects of methyl prednisolone administration. *Am Rev Respir Dis* 1990; **141**: 94–7.
56. Calandra T, Baumgartner JD, Grau GE *et al.* Prognostic values of tumor necrosis factor/cachectin, interleukin-1, interferon-alpha, and interferon-gamma in the serum of patients with septic shock. *J Infect Dis* 1990; **161**: 982–7.
57. Offner F, Philippe J, Vogelaers D *et al.* Serum tumor necrosis factor levels in patients with infectious disease and septic shock. *J Lab Clin Med* 1990; **116**: 100–5.
58. Waage A, Halstensen A, Espevik T. Association between tumor necrosis factor in serum and fatal outcome in patients with meningococcal disease. *Lancet* 1987; **i**: 355–7.
59. March CJ, Mosley B, Larsen A *et al.* Cloning, sequence and expression of two distinct human interleukin-1 complementary DNAs. *Nature* 1985; **315**: 641–7.
60. Kurt-Jones EA, Beller DI, Mizel SB, Unanue ER. Identification of a membrane associated interleukin 1 in macrophages. *Proc Natl Acad Sci U S A* 1985; **82**: 1204–8.
61. Beuscher HU, Fallon RJ, Colten HR. Macrophage membrane interleukin 1 regulates the expression of acute phase proteins in human hepatoma Hep3B cells. *J Immunol* 1987; **139**: 1896–901.
62. Matsushima K, Taguchi M, Kovacs EJ *et al.* Intracellular localization of human monocyte associated interleukin 1 (IL-1) activity and release of biologically active IL-1 from monocytes by trypsin and plasmin. *J Immunol* 1986; **136**: 2883–91.
63. Dinarello CA. Biology of interleukin 1. *FASEB J* 1988; **2**: 108–15.
64. Gery I, Davies P, Derr J *et al.* Relationship between the production and release of lymphocyte-activating factor (IL-1) by murine macrophages. I. Effects of various agents. *Cell Immunol* 1981; **131**: 293–303.
65. Oppenheim JJ, Stadler BM, Sirahanian RP *et al.* Lymphokines: their role in lymphocyte responses: properties of interleukin 1. *Federation Proceedings* 1982; **41**: 257–62.
66. Hesse DG, Tracey KJ, Fong Y *et al.* Cytokine appearance in human endotoxemia and primate bacteremia. *Surg Gynecol Obstet* 1988; **166**: 147–53.
67. Kasahara T, Mukaida N, Hatake K *et al.* Interleukin 1 (IL-1) dependent lymphokine production by human leukemic T cell line HSB.2 subclones. *J Immunol* 1985; **134**: 1682–9.
68. Kaye J, Gillis S, Mizel SB *et al.* Growth of a cloned helper T cell line induced by a monoclonal antibody specific for the antigen receptor: interleukin-1 is required for the expression of receptors for interleukin-2. *J Immunol* 1984; **133**: 1339–45.
69. Dinarello CA. Interleukin-1 and the pathogenesis of the acute-phase response. *N Engl J Med* 1984; **311**: 1413–18.
70. Zucali JR, Dinarello CA, Oblon DJ *et al.* Interleukin 1 stimulates fibroblasts to produce granulocyte–macrophage colony stimulating activity and prostaglandin E_2. *J Clin Invest* 1986; **77**: 1857–63.
71. van der Meer JWM, Barza M, Wolff SM, Dinarello CA. A low dose of recombinant interleukin 1 protects granulocytopenic mice from lethal Gram negative infection. *Proc Natl Acad Sci U S A* 1988; **85**: 1620–3.
72. Kampschmidt RF, Pulliam LA. Stimulation of antimicrobial activity in the rat with leukocyte endogenous mediator. *J Reticuloendothel Soc* 1975; **17**: 162–9.
73. Watson ML, Lewis GP, Westwick J. Increased vascular permeability and polymorphonuclear leucocyte accumulation *in vivo* in response to recombinant cytokines and supernatant from cultures of synovial cells treated with interleukin 1. *British Journal of Experimental Pathology* 1989; **70**: 93–101.
74. Schmidt JA, Oliver CN, Lepe-Zuniga JL *et al.* Silica stimulated monocytes release fibroblast proliferation factors identical to interleukin 1. A potential role for interleukin 1 in the pathogenesis of silicosis. *J Clin Invest* 1984; **73**: 1462–72.
75. Libby P, Warner SJC, Friedman GB. Interleukin 1: a mitogen for human vascular smooth muscle cells that induces the release of growth-inhibitory prostanoids. *J Clin Invest* 1988; **81**: 487–98.
76. Schlag G, Redl H, Hallström S. The cell in shock: the origin of multiple organ failure. *Resuscitation* 1991; **21**: 137–80.
77. Walter JS, Meyers P, Krueger JM. Microinjection of interleukin 1 into brain: separation of sleep and fever responses. *Physiol Behav* 1989; **45**: 169–76.
78. Oomura Y. Chemical and neuronal control of feeding motivation. *Physiol Behav* 1989; **44**: 555–60.
79. Shoham S, Davenne D, Cady AB *et al.* Recombinant tumor necrosis factor and interleukin 1 enhanced slow-wave sleep. *Am J Physiol* 1987; **253**: R142–9.
80. Uehara A, Gottschall PE, Dahl RR, Arimura A. Interleukin-1 stimulates ACTH release by an indirect action which requires endogenous corticotropin releasing factor. *Endocrinology* 1987; **121**: 1580–2.
81. Beach JE, Smallridge RC, Kinzer CA *et al.* Rapid release of multiple hormones from rat pituitaries perfused with recombinant interleukin-1. *Life Sci* 1989; **44**: 1–7.
82. Scarborough DE, Lee SL, Dinarello CA, Reichlin S. Interleukin-1β stimulates somatostatin biosynthesis in primary cultures of fetal rat brain. *Endocrinology* 1989; **124**: 549–51.
83. Roh MS, Drazenovich KA, Barbose JJ *et al.* Direct stimulation of the adrenal cortex by interleukin-1. *Surgery* 1987; **102**: 140–6.
84. Sandler S, Bentzen K, Borg LAH *et al.* Studies on the mechanisms causing inhibition of insulin secretion in rat pancreatic islets exposed to human interleukin-1β indicate a perturbation in the mitochondrial function. *Endocrinology* 1989; **124**: 1492–501.

85. Bachwich PR, Chensue SW, Larrick JW, Kunkel SL. Tumor necrosis factor stimulates IL-1 and PGE$_2$ production in resting macrophages. *Biochem Biophys Res Commun* 1986; **136**: 94–101.
86. Nawroth PP, Bank I, Handley D *et al.* Tumor necrosis factor interacts with endothelial cell receptors to induce release of IL-1. *J Exp Med* 1986; **13**: 1375.
87. Bevilacqua MP, Pober JS, Wheeler ME *et al.* Interleukin 1 acts in cultured human vascular endothelium to increase the adhesion of polymorphonuclear leukocytes, monocytes, and related leukocyte cell lines. *J Clin Invest* 1985; **76**: 2003–11.
88. Ramadori G, Sipe JD, Dinarello CA *et al.* Pretranslational modulation of acute phase hepatic protein synthesis by recombinant interleukin 1 (IL-1) and purified human IL-1. *J Exp Med* 1985; **162**: 930–42.
89. Tredget EE, Yu YM, Zhong S *et al.* Role of interleukin 1 and tumor necrosis factor on energy metabolism in rabbits. *Am J Physiol* 1988; **255**: E760–8.
90. Bevilacqua MP, Pober JS, Majeau GR *et al.* Interleukin 1 (IL-1) induces biosynthesis and cell surface expression of procoagulant activity in human vascular endothelial cells. *J Exp Med* 1984; **160**: 618–23.
91. Girardin E, Grau GE, Dayer JM *et al.* Tumor necrosis factor and interleukin-1 in the serum of children with severe infectious purpura. *N Engl J Med* 1988; **319**: 397–400.
92. Maury CPJ, Salo E, Pelkonen P. Circulating interleukin 1 beta in patients with Kawasaki disease. *N Engl J Med* 1988; **319**: 1670–1.
93. Miller LC, Dinarello CA. Biologic activities of interleukin-1 relevant to rheumatic diseases. *Pathol Immunopathol Res* 1987; **6**: 22–36.
94. Dinarello CA, Cannon JG, Mier JW *et al.* Multiple biological activities of human recombinant interleukin 1. *J Clin Invest* 1986; **77**: 1734–9.
95. Moldawer LL, Georgieff M, Lundholm K. Interleukin 1, tumour necrosis factor-alpha (cachectin) and the pathogenesis of cancer cachexia. *Clin Physiol* 1987; **7**: 263–74.
96. Wood JJ, Rodrick ML, Mannick JA *et al.* Inadequate interleukin 2 production: a fundamental immunological deficiency in patients with major burns. *Ann Surg* 1984; **200**: 311–20.
97. Grzelak I, Olszewski WL, Rowinski W. Blood mononuclear cell production of IL-1 and IL-2 following moderate surgical trauma. *Eur Surg Res* 1989; **21**: 114–22.
98. Abraham E, Richmond NJ, Chang YH. Effects of hemorrhage on interleukin 1 production. *Circ Shock* 1988; **25**: 33–40.
99. O'Riordain MG, Mannick JA, Rodrick ML *et al.* Modulation of macrophage hyperactivity improves survival in a burn–sepsis model. *Arch Surg* 1992; **127**: 152–8.
100. Tosato G, Seamon KB, Goldman ND *et al.* Monocyte-derived human B-cell growth factor identified as interferon-β_2 (BSF-2, IL-6). *Science* 1988; **239**: 502–4.
101. Gauldie J, Richards C, Harnish D *et al.* Interferon-β_2/B-cell stimulatory factor type 2 shares identity with monocyte-derived hepatocyte-stimulating factor and regulates the major acute phase protein response in liver cells. *Proc Natl Acad Sci U S A* 1987; **84**: 7251–5.
102. May LT, Santhanam U, Tatter SB *et al.* Phosphorylation of secreted forms of human β_2-interferon/hepatocyte stimulating factor/interleukin-6. *Biochem Biophys Res Commun* 1988; **152**: 1144–50.
103. Helfgott DC, May LT, Sthoeger Z *et al.* Bacterial lipopolysaccharide (endotoxin) enhances expression and secretion of β_2 interferon by human fibroblasts. *J Exp Med* 1987; **166**: 1300–9.
104. Fong Y, Moldawer LL, Marano M *et al.* Endotoxemia elicits increased circulating β_2-IFN/IL-6 in man. *J Immunol* 1989; **142**: 2321–4.
105. Wong GC, Clark SC. Multiple actions of interleukin 6 within a cytokine network. *Immunol Today* 1988; **9**: 137–9.
106. Garman RD, Jacobs KA, Clark SC, Raulet DH. B-cell stimulatory factor 2 (β_2 interferon) functions as a second signal for interleukin 2 production by mature murine T cells. *Proc Natl Acad Sci U S A* 1987; **84**: 7629–33.
107. Kishimoto T. Factors affecting B-cell growth and differentiation. *Annu Rev Immunol* 1985; **3**: 133–57.
108. Castell JV, Gómez-Lechón MJ, David M *et al.* Interleukin-6 is the major regulator of acute phase protein synthesis in adult human hepatocytes. *FEBS Lett* 1989; **242**: 237–9.
109. Nijsten MWN, DeGroot ER, Ten Duis HJ *et al.* Serum levels of interleukin-6 and acute phase responses. *Lancet* 1987; **ii**: 921.
110. Shenkin A, Fraser WD, Seris J *et al.* The serum interleukin-6 responses to elective surgery. *Lymphokine Res* 1989; **8**: 123–7.
111. Waage A, Brandtzaeg P, Halstensen A, Kierulf P, Espevik T. The complex pattern of cytokines in serum from patients with meningococcal septic shock. Association between interleukin 6, interleukin 1, and fatal outcome. *J Exp Med* 1989; **169**: 333–8.
112. Fry DE, Pearlstein L, Fulton RL *et al.* Multiple system organ failure. The role of uncontrolled infection. *Arch Surg* 1980; **115**: 136–40.
113. Polk HC Jr. Consensus summary on infection. *J Trauma* 1979; **19**: 894–6.
114. Curreri PW, Luterman A, Braun DW, Shires GT. Burn injury. Analysis of survival and hospitalization time for 937 patients. *Ann Surg* 1980; **192**: 472–8.
115. Sultzer BM. Genetic control of leukocyte responses to endotoxin. *Nature* 1968; **219**: 1253–4.
116. Filkins JP. Monokines and the metabolic pathophysiology of septic shock. *Federation Proceedings* 1985; **44**: 300–4.
117. Tracey KJ, Beutler B, Lowry SF *et al.* Shock and tissue injury induced by recombinant human cachectin. *Science* 1986; **234**: 470–4.
118. Gaskill HV III. Continuous infusion of interferon tumor necrosis factor: mechanisms of toxicity in the rat. *J Surg Res* 1988; **44**: 664–71.
119. Tracey KJ, Lowry SF, Fahey TJ III *et al.* Cachectin/tumor necrosis factor induces lethal shock and stress hormone responses in the dog. *Surg Gynecol Obstet* 1987; **164**: 415–22.
120. Tracey KJ, Lowry SF, Beutler B *et al.* Cachectin/tumor necrosis factor mediates changes in skeletal muscle plasma membrane potential. *J Exp Med* 1986; **164**: 1368–73.
121. Tracey KJ, Fong Y, Hesse DG *et al.* Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature* 1987; **330**: 662–4.
122. Beutler B, Milsark IW, Cerami AC. Passive immunization against cachectin/tumor necrosis factor protects mice from lethal effects of endotoxin. *Science* 1985; **229**: 869–71.
123. Luger A, Graf H, Scharz H *et al.* Decreased serum interleukin 1 activity and monocyte interleukin 1 production in patients with fatal sepsis. *Crit Care Med* 1986; **14**: 458–61.
124. van Deventer SJH, Büller HR, Ten Cate JW *et al.* Experimental endotoxemia in humans: analysis of cytokine release and coagulation, fibrinolytic and complement pathways. *Blood* 1990; **76**: 2520–6.
125. Fong Y, Tracey KJ, Moldawer LL *et al.* Antibodies to cachectin/TNF reduce interleukin-1β and interleukin-6 appearance during lethal bacteremia. *J Exp Med* 1989; **170**: 1627–33.
126. Starnes HF Jr, Pearce MK, Tewari A *et al.* Anti-IL-6 monoclonal antibodies protect against lethal *Escherichia coli* infection and lethal tumor necrosis factor-α challenge in mice. *J Immunol* 1990; **145**: 4185–91.
127. Crowley BM, Mannick JA, Rodrick ML *et al.* Antiendotoxin therapy improves survival in a model of thermal injury and sepsis. *Surgical Forum* 1990; **41**: 72–4.
128. Munster AM, Xiao GX, Guo Y *et al.* Control of endotoxemia in burn patients by use of polymyxin-B. *J Burn Care Rehabil* 1989; **10**: 327–30.
129. Ziegler EJ, McCutchan JA, Fierer J *et al.* Treatment of Gram-negative bacteremia and shock with human antiserum to a mutant *Escherichia coli*. *N Engl J Med* 1982; **307**: 1225–30.
130. Baumgartner JD, Glauser MP, McCutchan JA *et al.* Prevention of Gram negative shock and death in surgical patients by antibody to endotoxin core glycolipid. *Lancet* 1985; **ii**: 59–63.
131. Ziegler EJ, Fisher CJ, Sprung CL *et al.* Treatment of Gram-negative bacteremia and septic shock with HA-1A human monoclonal antibody against endotoxin. *N Engl J Med* 1991; **324**: 429–36.
132. Greenman RL, Schein RMH, Martin MA *et al.* A controlled clinical trial of E5 murine monoclonal IgM antibody to endotoxin in the treatment of Gram-negative sepsis. *JAMA* 1991; **266**: 1097–102.
133. Mathison JC, Wolfson E, Ulevitch RJ. Participation of tumor necrosis factor in the mediation of Gram negative bacterial lipopolysaccharide-induced injury in rabbits. *J Clin Invest* 1988; **81**: 1925–37.
134. Hinshaw LB, Tekamp-Olson P, Chang ACK *et al.* Survival of primates in LD100 septic shock following therapy with antibody to tumor necrosis factor (TNF-alpha). *Circ Shock* 1990; **30**: 279–92.
135. Exley AR, Cohen J, Buurman W *et al.* Monoclonal antibody to TNF in severe septic shock. *Lancet* 1990; **335**: 1275–7.
136. Schade UF. Pentoxifylline increases survival in murine endotoxin shock and decreases formation of tumor necrosis

factor. *Circ Shock* 1990; **31**: 171–81.

137. Arend WP. Interleukin 1 receptor antagonist. A new member of the interleukin 1 family. *J Clin Invest* 1991; **88**: 1445–51.
138. Dinarello CA, Thompson RC. Blocking IL-1: interleukin 1 receptor antagonist *in vivo* and *in vitro*. *Immunol Today* 1991; **12**: 404–10.
139. Alexander HR, Docherty GM, Buresh CM *et al.* A recombinant human receptor antagonist to interleukin 1 improves survival after lethal endotoxemia in mice. *J Exp Med* 1991; **173**: 1029–32.
140. Ohlsson K, Björk P, Bergenfeldt M *et al.* Interleukin-1 receptor antagonist reduces mortality from endotoxic shock. *Nature* 1990; **348**: 550–2.
141. Fischer CJ Jr, Slotman GJ, Opal T *et al.* Interleukin-1 receptor antagonist (IL-1RA) reduces mortality in patients with sepsis syndrome. *The American College of Chest Physicians. San Francisco, California, USA*. 3–6 November 1991 (Abstract).
142. Sheppard BC, Fraker DL, Norton JA. Prevention and treatment of endotoxin and sepsis lethality with recombinant human tumor necrosis factor. *Surgery* 1989; **106**: 156–62.
143. Echtenacher B, Falk W, Männel D, Krammer PH. Requirement of endogenous tumor necrosis factor/cachectin for recovery from experimental peritonitis. *J Immunol* 1990; **145**: 3762–6.

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Intra-abdominal photodynamic therapy: from theory to feasibility

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Photodynamic therapy is a new anticancer technique, directed at the selective destruction of neoplastic tissue, which has been used in the treatment of superficial or intraluminal lesions. The technique has now reached the stage where it can be considered in the peroperative management of gastrointestinal tumours, for example in an attempt to eradicate micrometastases in the tissue around the primary tumour or in residual lymph nodes after curative resection. Many practical problems remain to be solved, such as the pharmacokinetics of photosensitizers, the dosimetry of illumination and the sensitivity of intra-abdominal organs. An experimental and clinical evaluation is in progress to assess the feasibility of photodynamic therapy in surgical practice.

Photodynamic therapy (PDT) is an anticancer technique that has been known for a century[1] and which is increasingly applied in dermatology[2], urology[3], gastroenterology[4], ophthalmology[5] and neurosurgery[6]. It consists initially of systemic injection of a photosensitizer, which is preferentially taken up in tissues of strong mitotic activity and pathological stroma[7]. Photosensitizers develop no spontaneous toxicity; they must be excited by photons to produce cytotoxic free radicals, such as singlet oxygen or superoxide radicals[8]. The efficiency, relative selectivity and good tolerance of PDT raise the possibility of its use during intra-abdominal procedures to complement curative surgery. The limiting factor of an extensive parenchymal resection is the presence of micrometastases in the areolar tissue and in the lymph nodes. In spite of large visceral resections, micrometastases frequently remain and are responsible for either locoregional or metastatic recurrence[9–11].

It is worthy of note that the excitation of the photosensitizer by an incident photon produces re-emission of a fluorescent photon, which can be used to localize the reaction. Detection of this fluorescence may be of use in demonstrating small tumour deposits. A technique enabling both the visualization of micrometastases and their destruction will represent a significant advance. PDT is likely to contribute in both of these areas.

PDT is breaking new ground in oncological surgery. Nevertheless, it faces some difficulties in practical application. In particular, information is required about selective uptake of photosensitizer by malignant tissue, the appropriate conditions of exposure to the light beam and the tolerance of the normal surrounding organs. Although very few intra-abdominal pioneer studies have been conducted in humans, some theoretical and experimental data are now available to provide preliminary guidelines for the successful application of PDT for intra-abdominal use.

Scientific background

Concentration of photosensitizers in intra-abdominal organs

Each type of photosensitizing molecule has its own pattern of distribution in tissues. Nevertheless, most photosensitizers show a particular affinity for the reticuloendothelial system, and so the liver and spleen concentrate these molecules strongly. Gomer and Dougherty[12] studied the tissue distribution pattern of haematoporphyrin derivative (HpD) labelled with carbon-14 and tritium in the female DBA/2Ha$^-$DD mouse bearing a breast cancer. The tumour tissue retained the labelled HpD more than skin or muscle, but less than liver, kidney or spleen. The high hepatic and renal concentrations reflect the natural metabolism of porphyrin. Mang and Wieman[13] also observed a high concentration of Photofrin II (Photomedica, Raritan, New Jersey, USA) in normal pancreas of DBA/2HaRos$^-$d$^+$Ha mice. The clearance of tissues with relatively low affinity for HpD was fast (about 24–48 h) whereas for tissues with a strong affinity the concentration was still high at 72 h.

Tralau *et al.*[14] observed a concentration of aluminium sulphonated phthalocyanine (AlSPc) in the colon of the rat that was maximal between 1 and 3 h and progressively declined over 1 week. Aminolevulinic acid has recently been proposed to induce photosensitization by increasing the concentration of protoporphyrin IX in cells. The fluorescence in normal colonic tissue[15] was at a peak at 4 h with a rapid fall-off by 6 h and a return to background levels at 24 h.

In the pancreas of the Syrian golden hamster[14], the concentration of AlSPc reached a peak very rapidly after administration, declined over 48 h and rose again up to 1 week, finally falling to zero over 3 weeks. A high level of pheophorbide A in liver and spleen, falling logarithmically in 48 h, and a high concentration in the colon, peaking between 12 and 24 h, has recently been observed[16]. With pheophorbide A, concentration was less in the pancreas[17] with a rapid decrease over 24 h. Thus, pharmacokinetics of the available photosensitizers seem to be compatible with implementation of digestive tract PDT.

Selectivity of photosensitizers for intra-abdominal tumours

The selectivity ratio is used to express the relative concentration of photosensitizer in malignant as opposed to normal tissue. High ratios have been reported in different cancer models[18,19]. A ratio as high as 50:1 has been reported by Frigerio[20] in a brain tumour model. In cancers of the digestive tract, ratios seem not to be so high.

Agrev *et al.*[21] studied rats with dimethylhydrazine-induced colonic tumours and found a tumour:normal tissue concentration ratio of 1·8:1 at 72 h after intraperitoneal injection of HpD. Tralau *et al.*[14] reported a specificity ratio of 2·5:1 24–72 h after intravenous injection of AlSPc in tumours outside the central nervous system. Mang and Wieman[13] found a ratio of 1·5:1 at 24 h after intraperitoneal injection of HpD in an acinar pancreatic tumour and an identical ratio has been observed with pheophorbide A in the same tumour model[16]. A protoporphyrin IX ratio of 6:1 between tumour and normal colonic mucosa has been reported in the rat with aminolevulinic acid photosensitization[15].

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Table 1 *Doses of photodynamic therapy associated with recovery of normal intra-abdominal organs*

Reference	Organ	Species	Sensitizer	Wavelength (nm)	Delay for light exposure (h)	Power or energy density
Allardice *et al.*[23]	Ureter	Miniature piglet	HpD (5 mg/kg)	410–600	48	50 J/cm^2
Allardice *et al.*[23]	Colon	Miniature piglet	HpD (5 mg/kg)	410–600	48	50 J/cm^2
Barr *et al.*[24]		Rat	AlSPc (5 mg/kg)	675	1	50 J/cm^2
Douglass *et al.*[25]		Baboon	HpD (5 mg/kg)	631	48–96	36 J/cm^2
Bown *et al.*[26]	Liver	Rat	AlSPc and HpD (5 mg/kg)	675 and 630	A few minutes to 30 weeks	No tolerance
Douglass *et al.*[25]		Baboon	HpD (5 mg/kg)	631	48–96	No tolerance
Nuutinen *et al.*[27]	Bile duct	Hamster	AlS_2Pc (1 μmol/kg)	675	72	50 J
Douglass *et al.*[25]	Pancreas	Rabbit and baboon	HpD (5 mg/kg)	631	48–96	<144 J/cm^2
Mang and Wieman[13]		Mouse and hamster	HpD (40 mg/kg intraperitoneally)	630	24	270 J/cm^2
Nuutinen *et al.*[27]		Hamster	AlS_2Pc (1 μmol/kg)	675	72	50 J
Douglass *et al.*[25]	Stomach	Baboon and rabbit	HpD (5 mg/kg)	631	48–96	<144 J/cm^2
Nuutinen *et al.*[27]		Hamster	AlS_2Pc (1 μmol/kg)	675	72	50 J
Nuutinen *et al.*[27]	Duodenum	Hamster	AlS_2Pc (1 μmol/kg)	675	72	No tolerance
Suzuki *et al.*[28]	Large vessels	Rat	HpD (5 mg/kg)	628	48	100 J/cm^2
Nuutinen *et al.*[27]		Hamster	AlS_2Pc (5 μmol/kg)	675	72	50 J

Values correspond to tested values that are not necessarily equivalent to the photodynamic threshold of damage. HpD, haematoporphyrin derivative; AlSPc, aluminium sulphonated phthalocyanine; AlS_2Pc, disulphonated aluminium phthalocyanine

The theoretical requirement for PDT of a high tumour selectivity ratio is not supported by the observation of Fingar and Henderson[22], who showed benefit in avoiding recurrence when a margin of normal tissue around the tumour was destroyed to eradicate peripheral neoplastic cells. Moreover, a high ratio of selectivity is relevant only if the concentrations in normal tissues allow healing without unacceptable damage to structure or function. The tolerance of normal tissues around the tumour has to be considered in the assessment of locoregional toxicity of PDT (*Table 1*).

In vivo *toxicity of photosensitizers*

The systemic toxicity of photosensitizers is very low, particularly in comparison with chemotherapy and radiotherapy. It is noteworthy that no clinical or experimental renal, cardiac, hepatic, pulmonary or metabolic adverse drug reactions have been reported[2,29,30]. Franco *et al.*[31] have noticed some *in vitro* immune response depression by HpD, as well as bone marrow cellular hyperplasia and splenic hypertrophy. PDT seems slightly mutagenic (ten times less than radiotherapy) under *in vitro* experimental conditions, which is unrelated to its mode of action *in vivo*[32]. The only important adverse effect of PDT was skin photosensitization. Skin does not concentrate photosensitizers strongly, but it retains them for a long time[33]. Although the mean duration of photosensitization is 12 weeks, true sunburns have been observed 9 months after Photofrin II injection[33]. At present, the only treatment for this complication is prevention, but extensive research is being conducted in photoprotection. Repeated exposure of photosensitizers to light doses below threshold levels causes their destruction without oxidative reactions (photobleaching)[34]. This type of photoprotection may be of interest, but the results must be confirmed. At the same time pharmacological studies of the effects of sulphur compounds (M. Rougee, R. V. Bensasson, E. T. Land and R. Pariente, presented at the Société Française de Photobiologie meeting, Paris, 1988), prostaglandins (T. Patrice, M. T. Foultier and V. Praloran, presented at the Société Française de Photobiologie meeting, Paris 1988), antihistamine[33], cyano dyes[35] and radioprotectors[36] such as WR-2721 and WR-77913 are in progress.

Locoregional toxicity is an important consideration in the feasibility of intra-abdominal PDT and has been the subject of experimental evaluation. *Table 1* shows dose ranges that did not cause necrosis in various digestive organs submitted to different PDT protocols. The precise threshold of irreversible PDT damage is not known for each organ. Suzuki *et al.*[28] have treated the aortic region of Wistar rats by argon–rhodamine laser illumination with increasing light energies. No tissue damage (inflammatory cell infiltrates, interstitial oedema of vessels, vascular thrombus) was found in the non-photosensitized group. No histological change was noted in nervous tissue or muscle in rats receiving photosensitization. In contrast, changes in the vascular endothelium were observed in irradiated zones. At 6 h after irradiation, vascular endothelium had disappeared from large vessels, maximal lesion being observed at 24 h. The damage was greater in the lower vena cava than in the aorta; the magnitude of the lesion correlated with the dose of irradiation. Endothelial regeneration began on the third day after irradiation and was complete by day 5, with restitution of the vessel wall. The precise energy threshold at which parietal regeneration is impossible, with subsequent necrosis and rupture of the vessel, remains to be determined.

Barr *et al.*[24] studied the photodynamic action of AlSPc excited at 675 nm by an argon laser in the normal rat colon. The first lesions were vascular. Between 12 and 24 h, mucosal necrosis with inflammatory cell infiltrate was observed; the muscular layer was oedematous. Beyond 48 h, all layers of the centre of the exposed area were necrotic, but necrosis was limited to the mucosal and serosal layers at the periphery. Others have shown that the submucosal collagen layer is resistant to PDT but vulnerable to thermal injury[37]. Conservation of the submucosal matrix allowed regeneration of the mucosa and muscular layer. Healing of thermal lesions was by fibrosis[37]. Nevertheless, if necrotic lesions are circumferential, as would occur after treatment of the entire contents of the abdomen, it is possible that complications such as stricture may appear. However, Barr *et al.*[37] carried out electron microscopic studies, which showed conservation of the three-dimensional architecture of the collagen network and preservation of the periodicity of collagen microfibrils after PDT, whereas the fibrillar structure was lost after thermal injury. The bursting strength of the colon was not lowered after PDT; this suggests preservation of the collagen structure of the bowel wall. After thermal injury the bursting strength was significantly lowered.

That the liver is particularly sensitive to PDT has been shown by Douglass *et al.*[25] in rabbits and baboons. Hepatocytes in the immediate vicinity of peripheral portal triads show a greater resistance to necrosis. The intensity of damage in normal rat liver has been described by Bown *et al.*[26] with HpD as well as AlSPc. A highly pigmented organ such as the liver is hardly penetrated by the light beam. Necrosis of the hepatic parenchyma was obtained[26] to a depth of 0·5–4 mm with HpD excited at 630 nm and 1·5–8 mm for AlSPc excited at 675 nm. Hepatic clearance of AlSPc took considerably longer than that of HpD. This emphasizes the important variations in tissue affinity of different photosensitizers and highlights the need to tailor the photosensitizer to the target organ. Interestingly, oxygenation of the liver was essential for successful PDT; after vascular clamping, only hyperthermia could induce necrosis[26]. This suggests that vascular clamping of adjacent organs may be a potential photoprotective measure for the surrounding normal tissues.

In a preliminary paper, Douglass *et al.*[25] found that normal rabbit and baboon pancreas was particularly resistant to HpD irradiated at 631 nm. Mang and Wieman[13] have described the tolerance of normal Syrian golden hamster and mouse pancreas to dihaematoporphyrin ether (DHE) PDT. In spite of high concentrations of DHE similar to those observed in the reticuloendothelial system, the normal pancreas illuminated at 630 nm and 270 J/cm^2 showed no haemorrhage and no histological changes. This was confirmed by Schroder *et al.*[38] with HpD and by Nuutinen and co-workers[27] with disulphonated aluminium phthalocyanine (AlS_2Pc) in the same model. It has also been demonstrated[39] that normal pancreas did not develop pancreatitis in another model of acinar pancreatic carcinoma treated by pheophorbide A.

The potential toxicity of intra-abdominal PDT demands a precise knowledge of photosensitizer pharmacokinetics in the target and surrounding organs and of the tissue penetration of the laser beam. Photoprotection can then be achieved on the basis of differential tissue clearance, vascular clamping, shielding of sensitive organs and specific protection of non-malignant cells such as that given to normal hepatocytes by indocyanine green (T. Patrice, M. T. Foultier and V. Praloran, presented at the Société Française de Photobiologie meeting, Paris, 1988).

Light penetration in tissues

Penetration of target tissues by the irradiated light is another factor that limits the feasibility of intra-abdominal PDT. The behaviour of light through biological tissues is complex and is determined mainly by diffusion as predicted by mathematical models[40]. Tissue is always a heterogeneous mixture of fat, muscle, vessels, lymphatics, mucosa and so forth. Penetration in highly pigmented tissue such as the liver does not exceed 1–8 mm (depending on the photosensitizer used)[25,26]. The highest penetration of tissue in the visible spectrum is in the red and near-infra-red wavelengths. Barr *et al.*[41] reported necrosis to a depth of 5·5 mm in rat colonic mucosa, whereas Dougherty[42] estimated necrosis of 10 mm in interstitial PDT.

Penetration of green light is two or three times weaker than that of red[43], but green light activates photosensitizers more strongly. Studies are currently under way to test the direct use of a copper vapour laser, which can produce a high energy level, allowing a short exposure time[23,44].

A neodymium yttrium–aluminium–garnet Q-switched laser has been used to excite the photosensitizer molecule at 1060 nm by a two-photon simultaneous absorption phenomenon (excitation mode independent of the absorption spectrum of the molecule) to increase tissue penetration of PDT[45]. The biological effect produced (production of singlet oxygen) was much lower than that obtained by monophotonic excitation using green or red light[39].

Dosimetry

As for every application of PDT, *in situ* light delivery poses a practical problem. In particular, two difficulties to be solved are the choice of a light-delivery system and estimation of the effective dose delivered to the target. Light-delivery systems should: reach the target tissues even where there is difficult anatomical access, for example in the pelvic cavity; deliver uniform and homogeneous light; induce cell toxicity at the minimal energy level; and be of low cost and easy to maintain. Light can be delivered over a surface or by interstitial, intracavitary or intraluminal application.

Surface lighting is provided by a handpiece, which can be mobile or fixed. Lasers may be fitted with single- or multiple-strand quartz optical fibres, which are useful for application of PDT. The disadvantages of these systems include fibre–laser coupling[46], with an efficiency in light energy transmission of about 80 per cent, and a fall-off in light transmission along the bundle. To solve this problem, it is possible to use a microlens[47] at the fibre tip or to have the laser beam enter the fibre at an angle[48]. Instead of a handpiece, it is possible to have a fixed diffuser crystal at the end of the fibre, which allows the lighting of a predetermined target volume. In oncological surgery, peroperative PDT by surface lighting may be used for the sterilization of the operative field after visceral resection, especially where there is involvement of the serosa and lymph nodes.

Irradiation can be applied interstitially, but only in isotropic mode by the addition at the fibre tip of a small sphere of a very diffusive material such as polycarbonate, glass or microspheres. Simultaneous use of many fibres allows the treated volume and power delivered to be increased.

Intracavitary lighting is possible with cylindrical applicators of diffusive material placed at the end of the fibre. Covers can be incorporated into the cylinder to protect certain zones of the cavity and increase the power into the target volume[49]. In oncological surgery, cylindrical or hemicylindrical applicators may be considered in the treatment of the pelvic cavity after rectal resection, or of the mediastinum after oesophagectomy.

Finally, intraluminal irradiation is possible. Several cylindrical applicators 2–3 mm in diameter and 1–3 cm in length may be introduced into intraparenchymatous ducts or vessels, lighting a volume of solid viscus[48]. In oncological surgery, this technique may be utilized in portal veins or intrahepatic bile ducts to treat a volume of deep hepatic parenchyma. In conclusion, the choice of the device is indicated by the geometry of the target tissues and their translucency.

Control of the target dose is another fundamental problem of PDT. The theoretical model of light behaviour is extremely complex, involving the absorption coefficient, the diffusion coefficient and the angle of dispersion of the light[48]. Only absorbed energy produces a biological effect and the degree of tissue necrosis increases in proportion to the logarithm of the applied energy[50]. A light beam crossing a tissue can be reflected, transmitted, scattered or absorbed. Light distribution through various tissues is dominated by diffusion. After penetration of only 1 mm of tissue, diffusion is almost isotropic[48]. According to Wilson and Patterson[49], the optical properties of biological tissues are poorly understood. The depth of optical penetration depends on both tissue pigmentation and the wavelength of the light. Penetration of red light is two to three times greater than that of green. The dose delivered may be altered by either the power or the duration of irradiation. Power cannot be increased beyond the specification of the laser. Moreover, increasing power density would produce thermal effects, which might potentiate biological effects of PDT[51] but are quite different from them. Duration of irradiation, especially if the field to be treated is large, may be limited by the need to complete the surgical procedure. The maximum acceptable time required to perform intraoperative irradiation varies: Allardice *et al.*[23] required a maximum of 30 min, whereas Sindelar and colleagues[44] reported that it could take as long as several hours.

Intra-abdominal photodynamic therapy in practice

Experimental data

Very few experimental studies of intra-abdominal PDT have been published. The few reports do nevertheless allow a preliminary assessment of the diagnostic and therapeutic efficacy of the different available photosensitizers in relation to a given type of tumour. These investigations also permit an assessment of the efficiency of the light dose used and the extent of side-effects on normal tissues.

Diagnosis. Mang *et al.*[52], using a fluorimeter, were able to detect very small quantities of photosensitizer present in lymph nodes. These lymph nodes were invaded by subclinical metastases of PA-III prostatic adenocarcinoma of Pollard rats. These results, if reproduced by others, would open up interesting opportunities in the field of peroperative detection of micrometastases.

Therapy. Suzuki *et al.*[28] studied the Walker tumour model transplanted into the periaortic retroperitoneum of Wistar rats. The protocol of 5 mg/kg HpD plus irradiation at 628 nm, at 100 J/cm^2 for 80 mW, was compared with treatment in a control group that was only irradiated. In the controls neither haemorrhage nor necrosis was observed in either the tumour site or the retroperitoneum. In rats receiving HpD there was extensive tumour necrosis and collapse of tumour vessels. Large vessels, nerves and tissues around the tumour remained intact. In the HpD group, survival was significantly longer ($P < 0{\cdot}05$) than in the controls; one animal was apparently cured. According to Suzuki *et al.*[28], PDT seems to be particularly appropriate in the treatment of intra-abdominal tumours invading the retroperitoneum, particularly pancreatic cancer.

Mang and Wieman[13] have described the uptake and photobleaching kinetics of Photofrin II in an intraperitoneal model of azaserine-induced pancreatic tumour in Lewis rats and in pancreatic tumours induced in Syrian hamsters by 2,2′-dioxodi-*n*-propylnitrosamine. In both of these models, in contrast to observations in normal pancreas, tumour fluorescence diminished during irradiation and tumours became haemorrhagic. In other words, Photofrin II was simultaneously consumed by photobleaching and by photo-oxidation leading to cellular necrosis. The absence of photobleaching and photo-oxidation in normal pancreas was interesting; if this is confirmed, it may not be necessary to achieve a high tumour:normal tissue ratio of photosensitzer, and the tissue could be irradiated with a maximal tumour concentration of photosensitizer. Using the same cellular model implanted into the pancreatic tail of adult Lewis rats and a different photosensitizer (pheophorbide A)[39], a 66 per cent rate of complete remission 120 days after tumour implantation has been observed; all control animals were dead within 30 days. Because pancreatic cancer is likely to spread, not only in the retroperitoneum but also into the surrounding organs, the tolerance of these tissues to photodynamic protocols must be taken into account. In a study conducted in the Syrian golden hamster, Schroder *et al.*[38] and Nuutingen and colleagues[27] have shown that reversible damage occurred in the stomach and bile duct, but that the duodenum suffered necrotic damage leading to perforation after PDT with either DHE or AlS_2Pc.

Barr *et al.*[24] attempted selective destruction of a colonic tumour induced in Wistar rats by dimethylhydrazine. With an AlSPc dose of 5 mg/kg, non-selective destruction of both malignant and normal tissues occurred over a radius of 0·5 cm despite a photosensitizer ratio of 2:1. With one-tenth the dose, selective necrosis of 2 mm was achieved in tumour tissue. In normal tissues, AlSPc was photobleached before the threshold for PDT was reached.

Tochner *et al.*[53] treated malignant ascitis by PDT in female C3 HeB/FeJ mice after intraperitoneal injection of a malignant teratoma strain. This tumour develops intraperitoneally and induces ascites. Photofrin II 10 mg/kg was given intraperitoneally. A laser fibre introduced into the peritoneal cavity was used for irradiation 2 h later at 514 nm, at 10 mW for 16 min. This treatment was repeated on alternate days. Remission occurred in all animals, with definitive cure in 85 per cent. Three of the 20 mice died as a direct result of tumour spreading into the subcutaneous space along the track of the laser probe. There was no treatment-related bowel perforation. Even if experimental conditions are quite different from those of human carcinomatosis, this work demonstrates an interesting preliminary approach. Cancer deposits over the peritoneum are thin, at least in the early stages of disease. Therefore peritoneal deposits could be an appropriate target for intra-abdominal PDT.

The major criticism of all these murine models is their large difference of scale from human organs. Allardice *et al.*[23] recently reported a safety study for intraoperative PDT in the miniature piglet in which anatomical structures are of a similar size to those in humans. With a useful biological dose of PDT (HpD 5 mg/kg irradiated 48 h later by 50 J halogen light between 410 and 600 nm), no detrimental effects were observed on the healing of colonic and ureteric anastomoses. No ureteric stricture occurred.

Clinical data

To the authors' knowledge there are only four reports[29,44,46,54] of intra-abdominal PDT in humans. Three used peroperative PDT[29,44,46] and one postoperative[54].

Diagnosis. The diagnostic potential of PDT has been investigated. Although the fluorescence detection signal is limited by tissue autofluorescence[55,56], Herrera-Ornelas *et al.*[29] found an excellent correlation between observed sites of fluorescence and the presence of tumour in biopsies of the same sites. Clearly, further studies of sensitivity and specificity are necessary to determine the diagnostic importance of PDT.

Therapy. The first two studies were from the Roswell Park Memorial Institute at Buffalo, New York, USA. PDT was employed as adjuvant treatment after surgical debulking, but only at second-look surgery for recurrence. The first report[29] deals with the treatment of pelvic recurrence of colorectal cancer, the second[46] with retroperitoneal recurrence of liposarcoma.

The first report[29] was intended to be a feasibility study. PDT was used as adjuvant treatment in curative resection as well as in the palliation of surgically irresectable colorectal cancer recurrence. Fourteen patients received peroperative PDT; some of them also underwent postoperative PDT for pelvic recurrence following dehiscence of the pelvic wound. Irradiation was by a kiton red laser pumped by an argon laser. This system provided 4 W at 630 nm delivered through a quartz fibre of 400 nm linked to a microlens to homogenize the output beam. Up to four fibres could be used simultaneously for interstitial irradiation. The photosensitizer used was Photofrin 3 mg/kg, then Photofrin II 2 mg/kg. The power density was between 100 and 200 mW/cm^2. The duration of irradiation was 10–40 min, providing an irradiation dose of 100–400 J/cm^2. Tumour residues >1 cm deep were irradiated interstitially; sensitive organs such as the liver and kidneys were protected by covers. No local or systemic complication was observed after intravenous administration of HpD or DHE. Some minor skin reactions were reported in patients who did not take the recommended precautions; one second-degree burn of the perianal skin around the field of irradiation was the only complication. Fluorescence with Wood's rays was closely related to positive biopsies. Tumour sampling after PDT showed haemorrhagic necrosis. The results in terms of survival were poor, as expected in view of the patient selection. The practical advantage of PDT was that it did not produce any serious morbidity even in patients who had received radiotherapy. PDT was able to sterilize areas of microscopic tumour recurrence; furthermore, many patients experienced considerable relief of pelvic pain.

A second feasibility study[46] was performed by another surgical team in Buffalo. Retroperitoneal sarcomas were chosen because of their high recurrence rate in spite of apparently complete resection. Suzuki *et al.*[28] demonstrated low toxicity of PDT to neural tissue and muscle, which seems appropriate for retroperitoneal application. In a second-look study of ten patients with recurrence of sarcoma, Photofrin II was used at a dose of 2·5–5 mg/kg; illumination was by a kiton red laser emitting at 630 nm. A 400-nm quartz fibre with a microlens delivered an output of 3–4 W. The power density was 50–200 mW/cm^2 delivered for up to 20 min for a total light dose of 30–288 J/cm^2. Salmon pink tumour fluorescence was detected by an ultraviolet lamp. Patients were followed with computed tomography every 3 months. One died after operation from infection and haemorrhage not related to PDT. Two late (beyond 4 weeks) serious skin photosensitization accidents occurred. Two patients underwent complete surgical resection followed by irradiation of the tumour bed and were in total remission at 24 and 28 months. Three patients had a new recurrence in the margins of the treated zone; all others developed distant metastases but no local recurrence. This paper confirms the excellent tolerance of PDT and the value of tumour fluorescence in achieving total *en bloc* resection. The principal difficulty of the technique is the irradiation of the surgical field with the light source. To move the light source away to increase the area irradiated leads to a decrease in the energy delivered per unit area proportional to the square of the distance. The dose may be restored by increasing the exposure time to its square[29]. Multifibre lighting or plane geometry devices and more powerful laser sources are needed to reduce this time limitation.

The third study is a case report from Colombus, Ohio, USA[54]. A 57-year-old woman underwent cholecystectomy in 1985 and exploration revealed a common bile duct adenocarcinoma. A T tube was first inserted, followed by a U tube coursing through the skin. Intraluminal PDT was performed seven times during 4 years using a cylinder diffuser tip at the end of a quartz fibre. A choledochoscope was used to carry the fibre through the U tube. DHE was used at 2 mg/kg, 48–96 h before illumination. The laser was a kiton red dye laser pumped by an argon laser. Between 200 and 400 J were delivered per centimetre of diffusing tip. The biological tolerance to both DHE and PDT was excellent. The patient survived for more than 4 years, at which time metastases had appeared in the pleura.

The final published report, from the National Cancer Institute, Bethesda, Maryland, USA, was devoted to treatment of peritoneal carcinomatosis[44]. This phase I feasibility study was performed following experimental data showing cure by PDT in mice with peritoneal carcinomatosis[53]. Twenty-three patients with recurrent ovarian cancer and others with abdominal sarcomatosis or other type of cancer underwent surgical debulking of as much tumour as possible, leaving no neoplastic nodules of >5 mm. Two dye lasers emitting at 630 nm were used in tandem, delivering 1·5–7·5 W. The maximum delivered light dose was 3 J/cm^2, with a total energy delivered to each patient ranging from 2997 to 56 460 J. DHE was used as photosensitizer. A dilute lipid emulsion was employed to cover peritoneal surfaces and improve the homogenicity of dose delivery. Two different systems of light delivery were used. A flat-cut 0·6-mm optical fibre emitting a circular beam was held at a fixed distance by an adjustable clamp. A special wand consisting of a cylindrical diffusing tube permitted irradiation of the pelvis and abdominal wall. All intra-abdominal peritoneal surfaces were treated, with monitoring of light delivery by photodiodes. The mean duration of the procedure was 8·5 h. Five complications occurred following therapy: haemoperitoneum (one case), necrotizing pancreatitis (one), intestinal fistula (two) and urinoma (one). There was no postoperative death. It is difficult to determine the relative contribution of aggressive surgical debulking and PDT to these complications. Some reversible liver dysfunction and hypoalbuminaemia occurred after operation. Resolution of postoperative ileus and intra-abdominal fluid collection required up to 10 days. Of the 13 patients treated for ovarian cancer, 11 demonstrated progressive disease and two remained free of recurrence, at 8 and 14 months. Of the eight patients treated for sarcomatosis, two had no evidence of disease progression, at 8 and 9 months. Two patients treated for pseudomyxoma peritonei remained free of progressive disease, for 9 and 18 months.

Conclusions

The possibility of direct access to the malignant tumour makes the peroperative period a particularly opportune moment in the treatment of a patient with malignancy. The past decade has seen the development of therapeutic techniques such as peroperative irradiation and peroperative hyperthermic chemotherapy[57], designed as treatment adjuvant with resection of the macroscopic tumour. From both theoretical and experimental points of view, PDT seems to be able to play a complementary diagnostic and therapeutic role during resectional surgery. Peroperative PDT competes with intraoperative radiotherapy, which is undergoing clinical evaluation[58]. For the same therapeutic benefit, the advantages of PDT are numerous. Peroperative PDT has diagnostic properties, low morbidity, easier implementation and a much lower requirement for expensive equipment than radiotherapy.

Clinical evaluation of peroperative PDT is just beginning. The main practical problems to be solved are the extrapolation into clinical practice of experience acquired with animal models, and the definition of precise photodynamic protocols for the treatment of micrometastases of different digestive tract tumours without adverse reactions.

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References

1. Raab O. Über die wirkung fluoreszierender Stoffe auf Infusoria. *Zeitschrift für Biologie* 1900; **39**: 524–46.
2. McCaughan JD, Guy JT, Hicks W, Laufman L, Nims TA, Walker J. Photodynamic therapy for cutaneous and subcutaneous malignant neoplasms. *Arch Surg* 1989; **124**: 211–16.
3. Schumacker BP, Hetzel FW. Clinical laser photodynamic therapy in the treatment of bladder carcinoma. *Photochem Photobiol* 1987; **46**: 899–901.
4. Patrice T, Foultier MT, Adam F, Audoin AF, Galmiche JP, Le Bodic L. Traitement palliatif par photochimiothérapie de 54 cancers digestifs: essai clinique de phase 1. *Ann Chir* 1989; **43**: 433–7.
5. Murphree AL, Cote M, Gomer CJ. The evolution of photodynamic therapy techniques in the treatment of intraocular tumors. *Photochem Photobiol* 1987; **46**: 919–23.
6. Kostron H, Weiser G, Fritsch E, Grunert V. Photodynamic therapy of malignant brain tumors: clinical and neuropathological results. *Photochem Photobiol* 1987; **46**: 937–43.
7. Bugelski PJ, Porter CW, Dougherty TJ. Autoradiographic distribution of hematoporphyrin derivative in normal and tumor tissue of the mouse. *Cancer Res* 1981; **41**: 4606–12.
8. Foote CS. Light, oxygen and toxicity. In: Autor AP, ed. *Pathology of Oxygen.* New York: Academic Press, 1982: 21–44.
9. Warshaw AL, Swanson RS. Pancreatic cancer in 1988: possibilities and probabilities. *Ann Surg* 1988; **208**: 541–53.
10. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. *Lancet* 1986; **ii**: 996–9.
11. Gunderson LL, Sosin H. Adenocarcinoma of the stomach: areas of failure in a reoperation series (second or symptomatic look). Clinicopathologic correlation and implications for adjuvant therapy. *Int J Radiat Oncol Biol Phys* 1982; **8**: 1–11.
12. Gomer CJ, Dougherty TJ. Determination of [^{3}H] and [^{14}C] hematoporphyrin derivative distribution in malignant and normal tissue. *Cancer Res* 1979; **39**: 146–51.
13. Mang TS, Wieman TJ. Photodynamic therapy in the treatment of pancreatic carcinoma: dihematoporphyrin ether uptake and photobleaching kinetics. *Photochem Photobiol* 1987; **46**: 853–8.
14. Tralau CJ, Barr H, Sandeman DR, Barton T, Lewin MR, Bown SG. Aluminum sulfonated phthalocyanine distribution in rodent tumors of the colon, brain and pancreas. *Photochem Photobiol* 1987; **46**: 777–81.

15. Bedwell J, MacRobert AJ, Phillips D, Bown SG. A comparative study of distribution and photodynamic effect of ALA-induced PP IX in the rat colon. *Lasers in Medical Science* 1992; **7**: 32A.
16. Evrard S, Aprahamian M, Fukawa H *et al.* Localization of pheophorbide A in normal tissues and acinar pancreatic cancer in the rat. *Lasers in Medical Science* 1992; **7**: 107A.
17. Aprahamian M, Evrard S, Hajri A, Balboni G, Damgé C, Marescaux J. Intra-abdominal photodynamic therapy of an acinar pancreatic cancer: experimental study in the Lewis rat. *Digestion* 1990; **46**: 126A.
18. Dougherty TJ, Grindey GB, Weishaupt KR, Boyle D. Photoradiation therapy II: cure of animal tumors with hematoporphyrin and light. *J Natl Cancer Inst* 1975; **55**: 115–20.
19. Rasmussen-Taxdall DS, Ward GE, Figge FH. Fluorescence of human lymphatic and cancer tissues following high doses of intravenous hematoporphyrin. *Cancer* 1955; **8**: 78–81.
20. Frigerio NA. Metal phthalocyanines. US Patent 3 027 391, 27 March 1962.
21. Agrev MV, Wharen RE, Anderson RE *et al.* Hematoporphyrin derivative: quantitative uptake in dimethylhydrazine-induced murine colorectal carcinoma. *J Surg Oncol* 1983; **24**: 173–6.
22. Fingar VH, Henderson BW. Drug and light dose dependence of photodynamic therapy: a study of tumor and normal tissue response. *Photochem Photobiol* 1987; **46**: 837–41.
23. Allardice JT, Grahn MF, Rowland AC *et al.* Safety studies for intraoperative photodynamic therapy. *Lasers in Medical Science* 1992; **7**: 133–42.
24. Barr H, Tralau CJ, MacRobert AJ *et al.* Photodynamic therapy in the normal rat colon with phthalocyanine sensitisation. *Br J Cancer* 1987; **56**: 111–18.
25. Douglass HO, Nava HR, Weishaupt KR *et al.* Intra-abdominal applications of hematoporphyrin photoradiation therapy. *Adv Exp Med Biol* 1981; **160**: 15–21.
26. Bown SG, Tralau CJ, Coleridge Smith PD, Akdemir D, Wieman TJ. Photodynamic therapy with porphyrin and phthalocyanine sensitisation: quantitative studies in normal rat liver. *Br J Cancer* 1986; **54**: 43–52.
27. Nuutinen PJO, Chatlani PT, Bedwell J, MacRobert AJ, Phillips D, Bown SG. Distribution and photodynamic effect of disulphonated aluminium phthalocyanine in the pancreas and adjacent tissues in the Syrian golden hamster. *Br J Cancer* 1991; **64**: 1108–15.
28. Suzuki S, Nakamura S, Sakaguchi S. Experimental study of intra-abdominal photodynamic therapy. *Lasers in Medical Science* 1987; **2**: 195–203.
29. Herrera-Ornelas L, Petrelli NJ, Mittelman A, Dougherty TJ, Boyle DG. Photodynamic therapy in patients with colorectal cancer. *Cancer* 1986; **57**: 677–84.
30. Dougherty TJ, Kaufmann JE, Goldfarb A. Photoradiation therapy for the treatment of malignant tumors. *Cancer Res* 1978; **38**: 2628–35.
31. Franco P, Nicolin L, Ricci F. *In vitro* hematoporphyrin inhibitory effects on some immunological assays. *Int J Immunopharmacol* 1983; **5**: 533–40.
32. Evensen JF, Moan J. Photodynamic action and chromosomal damage: a comparison of hematoporphyrin derivative (HPD) and light with X-irradiation. *Br J Cancer* 1982; **45**: 456–65.
33. Manyak MJ, Smith PD, Harrington FS, Steinberg SM, Glatstein E, Russo A. Protection against dihematoporphyrin ether photosensitivity. *Photochem Photobiol* 1988; **47**: 823–30.
34. Boyle DG, Potter WR. Photobleaching of Photofrin II as a means of eliminating skin photosensitivity. *Photochem Photobiol* 1987; **46**: 997–1001.
35. Kita K, Itoshima T, Ito T *et al.* Photodynamic therapy of rat liver cancer: protection of the normal liver by indocyanine green. *Gastroenterol Jpn* 1987; **22**: 464–73.
36. Dillon J, Kennedy JC, Pottier RH. *In vitro* and *in vivo* protection against phototoxic side effects of photodynamic therapy by radioprotective agents WR-2721 and WR-77913. *Photochem Photobiol* 1988; **48**: 235–8.
37. Barr H, Tralau CJ, Boulos PB, MacRobert AJ, Tilly R, Bown SG. The contrasting mechanisms of colonic collagen damage between photodynamic therapy and thermal injury. *Photochem Photobiol* 1987; **46**: 795–800.
38. Schroder T, Chen IW, Sperling M, Bell RH, Brackett K, Joffe SN. Hematoporphyrin derivative uptake and photodynamic therapy in pancreatic carcinoma. *J Surg Oncol* 1988; **38**: 4–9.
39. Evrard S, Jeannin E, Tsuji M, Damgé C, Marescaux J, Aprahamian M. Photodynamic therapy (PDT) of a pancreatic cancer in the rat. *Br J Surg* 1992; **79S**: 75A.
40. Wilson BC, Adam G. A Monte Carlo model for the absorption and flux distributions of light in tissue. *Med Phys* 1983; **10**: 824–30.
41. Barr H, Tralau CJ, Lewin M, Clark CG, Bown SG, Boulos PB. Selective destruction of experimental colon cancer using photodynamic therapy. *Br J Surg* 1988; **75**: 611–12.
42. Dougherty TJ. Photodynamic therapy. In: Jori G. Perria C, eds. *Photodynamic Therapy of Tumors and Other Diseases.* Padua: Libreria Progetto, 1985: 267–80.
43. Svaasand LO, Doiron DR. Thermal distribution during photoradiation therapy. In: Kessel D, Dougherty TJ, eds. *Porphyrin Photosensitization.* New York: Plenum Press, 1983: 77–90.
44. Sindelar WF, DeLaney TF, Tochner Z *et al.* Technique of photodynamic therapy for disseminated intraperitoneal malignant neoplasms. *Arch Surg* 1991; **126**: 318–24.
45. Mashiko S, Sato S, Inaba H, Taguchi Y, Kasai M, Kimura S. Basic study on photochemical effect of pheophorbide A irradiated by NdYAG light. *Journal of the Japanese Society for Laser Medicine* 1985; **6**: 113–16.
46. Nambisan RN, Karakousis CP, Holyoke ED, Dougherty TJ. Intraoperative photodynamic therapy for retroperitoneal sarcomas. *Cancer* 1988; **61**: 1248–52.
47. Doiron DR. Photophysics of and instrumentation for porphyrin detection and activation. In: Doiron DR, Gomer CJ, eds. *Porphyrin Localization and Treatment of Tumors.* New York: Alan R Liss, 1984: 41–74.
48. McKenzie AL. How may external and interstitial illumination by compared in laser photodynamic therapy? *Phys Med Biol* 1985; **30**: 455–60.
49. Wilson BC, Patterson MS. The physics of photodynamic therapy. *Phys Med Biol* 1986; **31**: 327–60.
50. Pimstone NR, Gandhi SN. Optimal photodynamic band of red light in hematoporphyrin derivative (HpD) photoradiation therapy of cancer. *Prog Clin Biol Res* 1984; **170**: 673–8.
51. Henderson BW, Waldow SM, Mang TS, Dougherty TJ. Photodynamic therapy and hyperthermia. In: Jori G, Perria C, eds. *Photodynamic Therapy of Tumors and Other Diseases.* Padua: Libreria Progetto, 1985: 183–93.
52. Mang TS, Potter WR, Dougherty TJ. Fluorescence detection in occult metastases of the lymph nodes following injection of low levels of dihematoporphyrin ethers. *Photochem Photobiol* 1984; **39S**: TAM-C8 (Abstract).
53. Tochner Z, Mitchell JB, Smith P *et al.* Photodynamic therapy of ascites tumours within the peritoneal cavity. *Br J Cancer* 1986; **53**: 733–6.
54. McCaughan JS, Mertens BF, Cho C, Barabash RD, Payton HW. Photodynamic therapy to treat tumors of the extrahepatic biliary ducts. *Arch Surg* 1991; **126**: 111–13.
55. Baumgartner R, Fisslinger H, Jocham D *et al.* A fluorescence imaging device for endoscopic detection of early stage cancer: instrumental and experimental studies. *Photochem Photobiol* 1987; **46**: 759–63.
56. Balchum OJ, Profio AE, Razum N. Ratioing fluorometer probe for localizing carcinoma *in situ* in bronchi of the lung. *Photochem Photobiol* 1987; **46**: 887–91.
57. Kaibara N, Hamazoe R, Iitsuka Y, Maeta M, Koga S. Hyperthermic peritoneal perfusion combined with anti-cancer chemotherapy as prophylactic treatment of peritoneal recurrence of gastric cancer. *Hepatogastroenterology* 1989; **36**: 75–8.
58. Bail JP, Etienne J, Robaszkiewicz M *et al.* La radiothérapie intra-opératoire en cancérologie digestive. *Gastroenterol Clin Biol* 1989; **13**: 388–96.

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Digest

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Continuing our exchange with the German journal Der Chirurg, *Professor Christian Herfarth and Dr Thomas Lehnert have selected from the last 3 months of 1992 for their resumé.*

Portal hypertension

Bleeding from oesophageal varices is associated with a high mortality rate in patients with cirrhosis. In Child's grades B and C the mortality rate of each bleeding episode can be as high as 40 and 70 per cent respectively. The risk of rebleeding can be lowered in such patients by portosystemic shunting. These patients may, however, be candidates for subsequent liver transplantation and the risk of this is considerably higher in those who have undergone previous abdominal surgery. An alternative approach is to decrease portal pressure by transjugular intrahepatic portosystemic shunts using transluminally introduced stents. The jugular vein is cannulated and a guidewire introduced into the right or middle hepatic vein. Following transparenchymal advancement of the wire the portal vein is cannulated. The liver parenchyma is then dilated with a bougie until a stent can be introduced to connect the systemic and portal circulations. The diameter of the stent can be varied until the desired pressure gradient is achieved.

At the time of the present report[1] this technique has been successfully used in 50 patients. Otto and associates now report the first two patients from their series in whom liver transplantation was performed subsequent to transjugular intrahepatic portosystemic shunting. In both patients portal pressure was reduced, from 26 to 16 mmHg and from 27 to 15 mmHg, using 10-mm stents. Orthotopic liver transplantation was successfully performed after 2 and 3 months respectively. The authors compared initial experience with transjugular intrahepatic portosystemic shunting to that in eight patients in whom liver transplantation was performed after a previous surgical portosystemic shunt. The operative procedure was considerably facilitated if portal pressure had been reduced by intrahepatic stent shunts compared with transplantation in patients with surgical shunts.

Anorectal incontinence

For successful treatment of anorectal incontinence a diligent diagnostic evaluation of the possible causes is essential. Athanasiadis[2] studied the value of electromyography of the anal sphincter muscle in 14 female patients with clinical signs of faecal incontinence and compared the findings with those in 14 healthy women. Significant differences were found between patients and controls regarding the duration of action potentials, average amplitude and the frequency of polarity reversals. With the help of computer-assisted analysis of electromyographic data, neurogenic and myogenic disturbances were distinguished and the functional integrity of the external anal sphincter and puborectalis muscle analysed. This technique should help to define indications for surgical repair better and aid evaluation of the success of different surgical approaches.

Peritonitis

A group from Aachen[3] evaluated recent experience with the treatment of peritonitis. Between January 1986 and June 1990 a total of 260 procedures were listed in association with peritonitis in a computer database. Some 183 operations were performed on 96 patients with diffuse peritonitis. The most frequent source of peritonitis was the colorectum, accounting for 30 per cent of all cases; the next most common lesions were of the small bowel, stomach and duodenum. Despite efforts to improve early diagnosis, in almost 20 per cent of patients ($n = 17$) the cause of diffuse peritonitis was appendicitis. Only two of these 17 patients developed diffuse peritonitis following appendicectomy (one each after laparoscopic and open operation). Treatment was based on clinical assessment of the severity of peritonitis. Low-grade peritonitis ($n = 52$) was treated by intraoperative lavage using 9–12 litres saline followed by drainage of all four abdominal quadrants. Moderate peritonitis ($n = 23$) was treated by continuous peritoneal lavage with various solutions according to the patient's overall status. The average daily lavage volume was 24 litres and the duration of the lavage 48 (range 24–216) h. Patients with severe diffuse peritonitis ($n = 21$) were treated by reoperation or open dorsoventral lavage. The overall mortality rate in the 96 patients was 32 per cent, with the highest mortality rate in those with liver and gallbladder (two of four) or the small bowel (11 of 23) as sources of diffuse peritonitis. The mortality rate for patients with postoperative peritonitis was 38 per cent (12 of 32). The authors compared the results with a projected outcome using a classification based on the Mannheim peritonitis index. Patients treated by a standard regimen, continuous peritoneal lavage or treatment by open abdomen fared better than expected. The authors concluded that a staged surgical approach based on the severity of diffuse peritonitis has the potential to improve results of treatment.

Pulmonary embolism

Pulmonary embolism remains a life-threatening complication in the postoperative period. Schürmann and colleagues[4] from Munich retrospectively analysed the clinical course and outcome of patients with pulmonary embolism treated between 1978 and 1986. A diagnosis of pulmonary embolism was confirmed by review of post-mortem results and/or findings at lung perfusion scintigraphy. A total of 296 patients were identified, 260 of whom were inpatients, representing an incidence of 0·55 per cent during the 9-year study period. Some 93 pulmonary embolisms were diagnosed by lung perfusion scintigraphy; only 28 of 203 found on post-mortem examination had been diagnosed clinically. The authors classified embolism into three groups: involvement of no more than one segment; involvement of no more than one lobe; and involvement of more than one lobe. The majority of emboli were located in the lower segments of the lung and 26 patients had complete occlusion of pulmonary arteries. Interestingly, 20 per cent of patients diagnosed at post mortem were in the most severe category with involvement of at least one complete lobe of the lung compared with only 13 per cent of those diagnosed by perfusion scintigraphy. One reason for this may be that patients with extensive embolism were too ill to undergo scintigraphic studies. This is supported by the finding that all patients diagnosed by scintigraphy survived. Pulmonary embolism was considered a direct cause of death in 13 per cent of patients and in another 23 per cent was deemed to have contributed significantly to a fatal outcome. The highest incidence of

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pulmonary embolism (1·5 per cent) was recorded in patients undergoing abdominal procedures for septic conditions. The next highest incidence was after vascular surgery (0·9 per cent); following trauma surgery the incidence was only 0·2 per cent. Aortic operations were associated with a particularly high risk of 2·1 and 4·8 per cent for procedures on the abdominal and thoracic aorta respectively. Embolism was diagnosed earlier in the postoperative period in patients undergoing vascular procedures than in the other groups. Venous thrombosis as a possible cause of pulmonary embolism was demonstrated in 198 patients. In a large number venous thrombosis was present in the upper extremities alone ($n = 61$) or in combination with thrombotic lesions of the lower extremities ($n = 41$). In 46 patients, post-mortem examination implicated central venous catheters as the leading cause of peripheral thrombus formation.

Endoscopic surgery

Fromont and Leroy[5] from France reported thoracoscopic pulmonary lobectomy in a 40-year-old man with biopsy-proven adenocarcinoma of the middle lobe of the right lung. The patient was positioned as for posterolateral thoracotomy. Four cannulas were introduced: one of 10 mm in the posterior axillary line of the seventh intercostal space for the camera, one of 10 mm in the mid-axillary line of the ninth intercostal space for clips, scissors, cautery, etc., one of 5 mm in the mid-axillary line of the fifth intercostal space for an atraumatic forceps and one of 5 mm in the anterior axillary line of the fourth intercostal space for another atraumatic forceps. Using double-lumen intubation the right lung was collapsed. Dissection started laterally along the planes of the interlobar space with a monopolar 35-W electrocautery hook. After isolation of the middle lobe artery this was divided using a 30-mm Endo-GIA stapler (US Surgical, Norwalk, Connecticut, USA). The bronchus was dissected free and divided with the Endo-GIA before dealing with the lobar vein. The lobe was removed through the extended incision in the seventh intercostal space made to introduce the camera. The postoperative course was uneventful and the patient was discharged on the sixth day. Histological examination revealed a well differentiated adenocarcinoma 6 cm in diameter. The thoracoscopic procedure reduced postoperative pain and hospital stay but its safety and efficacy will have to be evaluated.

Hazards of laparoscopic procedures continue to be identified. Mastragelopulos and colleagues[6] from Karlsruhe reported the case of a 37-year-old woman with venous bleeding from the gallbladder bed following subtotal cholecystectomy for symptomatic gallbladder stones. An attempt was made to control venous bleeding using an argon-beam laser. After adjusting the instrument tip the argon laser was ignited automatically. A few seconds later a sudden drop in systolic blood pressure from 130 to 65 mmHg was recorded together with tachycardia. Oxygen saturation was reduced by 50 per cent and end-expiratory carbon dioxide dropped to 16 mmHg. The patient recovered rapidly following volume replacement and increase of inspired oxygen to 100 per cent. As bleeding continued, immediate laparotomy was performed. The right lobe of the liver showed livid discoloration which resolved within 1 min. In the gallbladder bed a 3-mm venous branch draining immediately into a large-calibre segmental vein was identified. When pressure was applied gas bubbles emptied from the vein. The vessel was oversewn and bleeding was controlled satisfactorily. The patient's further course was uneventful and she was discharged on the seventh day after operation. The authors concluded that the episode was caused by argon gas embolization and urged caution in the use of argon-laser coagulation in laparoscopic surgery.

Pulmonary failure

Pulmonary failure in patients in surgical intensive care occurs in between 10 and 60 per cent, with an associated mortality rate of 50–90 per cent. In patients with mechanical respiratory support, pulmonary atelectasis develops in the dorsal parts of the lung if the patients are positioned in a supine position. Walz and Muhr[7] from Bochum reported experience with alternate prone and supine positioning of 16 patients requiring mechanical ventilation. The authors used the technique both in patients with isolated severe thoracic trauma and in those with multiple injuries. Patients were eligible if they developed adult respiratory distress syndrome. No definite criteria for alternate positioning were established but the technique was used when positive end-expiratory pressure and inversed-ratio ventilation were not successful in reducing the inspired oxygen fraction (F_{IO_2}) to $\leqslant 0{\cdot}4$. A special bed allowing rotation of the patient in the vertical axis (Circ-O-lectric Bed; Stryker, Mülheim/Ruhr, Germany) was used. A self-constructed bed allowing rotation in the longitudinal axis has been developed and this allows safe rotation of patients with unstable spinal injuries. The authors emphasize that it is of utmost importance to ensure adequate bolstering of the patient's head with individually tailored cushions. The report details 16 men with an average age of 41·3 years and impending or manifest pulmonary failure. All but one were trauma victims and eleven had severe blunt thoracic trauma. The average Injury Severity Score was 30 (range 15–50). Alternate positioning commenced at an average of 9·5 days after admission and continued for a mean of 15·4 (range 7–32) days. The average F_{IO_2} was 0·54 at the start of alternate positioning and was reduced by an average of 0·2 within the first 48 h of treatment. Arterial oxygen saturation typically decreased during the first 30–60 min after prone positioning then rose and reached a plateau before falling again. This second decrease in oxygen saturation was used as an indicator to reverse the prone position and continue respiratory support in the supine position. The mean duration of prone positioning was 6·3 (range 4·5–20) h. Computed tomography was performed in six patients and revealed dorsal atelectasis in the supine position which completely resolved when prone without demonstration of corresponding ventral atelectasis.

Eleven of the sixteen patients survived. The cause of death in five patients was severe sepsis, with myocardial failure in two and multiple organ failure in three. No patient died from isolated pulmonary failure.

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References

1. Otto G, Richter GM, Theilmann L *et al.* Liver transplantation following transjugular intrahepatic portosystemic stented shunt. *Chirurg* 1992; **63**: 730–2.
2. Athanasiadis S. Electromyographic findings in pelvic floor muscles of patients with anorectal incontinence. *Chirurg* 1992; **63**: 822–6.
3. Winkeltau G, Winkeltau GU, Klosterhalfen B, Niemann H, Treutner KH, Schumpelick V. Selective surgical management of diffuse peritonitis. *Chirurg* 1992; **63**: 1035–40.
4. Schürmann M, Stiegler H, Riel KA, Schildberg FW. Pulmonary embolism in surgical patients. *Chirurg* 1992; **63**: 811–16.
5. Fromont G, Leroy J. Thoracoscopic pulmonary lobectomy. *Chirurg* 1992; **63**: 1050–2.
6. Mastragelopulos N, Sarkar MR, Kaissling G, Bähr R, Daub D. Argon gas embolism during laparoscopic cholecystectomy using the argon-beam-one coagulator. *Chirurg* 1992; **63**: 1053–4.
7. Walz M, Muhr G. Alternate prone and supine positioning in patients with acute respiratory failure. *Chirurg* 1992; **63**: 931–7.

Digest

SURGERY TODAY
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A selection of the best of Surgery Today (The Japanese Journal of Surgery) *from July, September and November 1992, written by the Editor-in-Chief, Professor Yoshio Mishima.*

Gallbladder

Sakurai *et al.*[1] quantified the adherence of *Escherichia coli* and *Pseudomonas aeruginosa* to the epithelium of gallbladders obtained from 32 patients with negative bile culture using a scanning electron microscope. Of the gallbladders, five were histologically normal (group A), 21 had chronic calculus cholecystitis (group B) and six had acute calculus cholecystitis (group C). The data were expressed as the number of adherent bacteria per $1000\,\mu m^2$ of gallbladder epithelium. The mean(s.d.) number of adherent *E. coli* was 0·1(0·2) in group A, 4·2(2·8) in group B and 9·2(3·3) in group C. A similar result was observed with *P. aeruginosa*. The number of adherent bacteria of both types was significantly higher in group C than groups A and B, and was significantly higher in group B compared with group A. Bacterial adherence correlated with the degree of epithelial damage. Normal epithelium had an inhibiting ability. Secondary bacterial infection is, therefore, more likely in patients with contaminated bile, and the treatment for acute cholecystitis should be based on the results of bile culture or according to predictive factors for bacterial colonization of bile.

Gastric cancer

Yonemura and colleagues[2] analysed paraffin-embedded tumour samples from 151 patients with stage I gastric cancer by DNA flow cytometry. Eighty patients received an infusion of 5-bromo-2′-deoxyuridine (BrdU) to determine the fraction in S phase. The S-phase fractions of tumours were measured by an immunohistochemical method using an anti-BrdU monoclonal antibody. Of the 151 patients, 81 (54 per cent) and 70 (46 per cent) had tumours with diploid and aneuploid patterns respectively. There was no correlation between DNA ploidy and wall invasion, histological type or lymphatic invasion. Aneuploid tumours were associated with positive vessel invasion. When DNA ploidy and clinicopathological parameters were simultaneously entered into a Cox regression model, ploidy and wall invasion emerged as independent prognostic parameters. Aneuploid tumours had significantly higher BrdU labelling indices than diploid lesions. The results indicate that determination of DNA ploidy patterns may be an important prognostic factor in patients with stage I gastric cancer and may be useful in guiding therapy.

Matsui *et al.*[3] investigated oestrogen (ER) and progesterone (PR) receptors immunohistologically in 107 patients with gastric cancer undergoing curative resection. ER and PR were detected only in the cancer cell nucleus. The ER-positive rate was 28 per cent for men and 31 per cent for women, while the proportions positive for PR were 9 and 12 per cent respectively. Clinicopathologically, the ER-positive rate was slightly higher in young women and in those with poorly differentiated gastric cancer. When survival was analysed in relation to the presence or absence of receptors, the 10-year cumulative survival rate after surgery was significantly lower in patients with ER-positive tumours than in those with ER-negative lesions (16 *versus* 63 per cent) and also significantly lower in those positive for PR than in those negative for this receptor (18 *versus* 48 per cent). The coexistence of ER and PR in gastric cancer tissue suggests that the former receptor is physiologically active, or that ER-positive gastric cancer is hormone dependent.

Sakamoto and co-workers[4] analysed the prognostic value of immunosuppressive acidic protein (IAP), known to suppress various immune responses in patients with cancer, in a prospective randomized trial of patients with advanced gastric cancer. The effect of polysaccharide K (PSK, Krestin; Sankyo, Tokyo, Japan), a type of biological response modifier with protein-bound polysaccharides, was also studied. Preoperative serum IAP levels were determined in 228 patients undergoing radical gastric resection; the tests were conducted in one laboratory by the single radial immunodiffusion method. All patients were followed for ≥ 24 months. There was an overall significant difference in disease-free survival time in favour of the PSK-treated group compared with controls. Preoperative IAP values correlated with disease-free survival time. An appropriate cut-off level for IAP was determined using Cox's proportional hazards model; the most significant difference was observed at a threshold concentration of $580\,\mu g/ml$. Patients receiving PSK with a preoperative IAP level $< 580\,\mu g/ml$ showed an improved disease-free survival rate ($P = 0{\cdot}03$). No significant difference was seen between the two groups when the preoperative IAP exceeded the cut-off level. PSK is likely to be most effective in patients whose preoperative IAP level is lower than this threshold value.

Umehara *et al.*[5] studied the amounts of nuclear DNA in gastric cancer metastases histologically and cytochemically by flow cytometry performed retrospectively on paraffin-embedded specimens from 95 patients. At surgery, all patients with aneuploid tumours had lymph node metastases. Liver metastases were frequently seen in those with aneuploid cancers (63 per cent; $P < 0{\cdot}01$), while lung metastases were the most common in those with diploid tumours (50 per cent; $P < 0{\cdot}05$). The incidence of peritoneal metastasis was high in patients with undifferentiated diploid cancers (72 per cent; $P < 0{\cdot}01$). Local lymph node recurrence was more common in those with aneuploid than diploid tumours ($P < 0{\cdot}01$). The incidence of bone and distant lymph node metastasis was found to be strongly dependent on tissue differentiation. DNA ploidy pattern is, therefore, correlated with lymph node, liver and lung metastases in patients with gastric cancer.

Paediatrics

Flow cytometric DNA content analyses were performed by Naito and colleagues[6] on samples from 72 patients with neuroblastoma. Nuclear suspensions obtained from paraffin-embedded samples were prepared using the method described by Schutte *et al.*[7]. Determination of DNA ploidy was possible in 62 patients: diploidy was detected in 23 (37 per cent) and aneuploidy in 39 (63 per cent). Cell sorting was performed on two peak areas of the DNA histogram of samples showing aneuploidy. The sorted cells of the first peak area were small and round and considered to be normal lymphocytes. The cells of the second peak were relatively large with obvious nucleoli; they were believed to be neuroblastoma cells. It was concluded that cell sorting may be of benefit in giving detailed information about DNA histograms, even in samples obtained from paraffin-embedded tissue.

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Intestinal disease

Thirty-seven patients with Crohn's disease underwent intraoperative endoscopy during resection of affected intestine in a study by Arima *et al.*[8]. The mean age of the patients at surgery was 23·2 years. The residual lesions in the remaining intestine identified by intraoperative endoscopy were classified according to their pathological profiles into three groups. In group A, comprising patients with longitudinal ulcers and/or bowel of cobblestone appearance, ten of 12 patients had recurrence. In five of these ten, the residual lesions were exacerbated and two patients required further surgery. The remaining five patients showed recurrence at the site of previous anastomosis and two of these five required additional surgery. In group B, made up of patients with small ulcers, aphthoid ulcers or scars, and group C, comprising those with no residual lesions, recurrence was observed in 13 of 16 and three of nine patients respectively. The recurrent lesions were all found proximal to, or at the site of, previous anastomosis. Additional operations were performed on three of the group B patients. The findings of this study reveal that recurrence requiring additional surgery is more frequent at the site of anastomosis regardless of the endoscopic appearance of the residual lesions.

In the controversy over whether sphincter-saving excision or abdominoperineal resection (APR) is more appropriate for the treatment of very low rectal cancer, local recurrence rates seem to play a fundamental role in patient outcome. To operate an effective patient selection policy, very low rectal cancer was defined as that located within 4·5–7·5 cm of the anal verge. Tuscano *et al.*[9] reported the incidence of local recurrence after curative surgery for very low rectal carcinoma in 24 consecutive patients treated by the same surgical team over a 15-year period using the above surgical procedures. In patients undergoing APR the local recurrence rate was 45 per cent (five of 11 patients); in those receiving sphincter-saving resection it was 46 per cent (six of 13), with no significant difference between the two groups. Recurrence was found within 1 year of surgical treatment in all except one patient. Despite the strict follow-up programme, it was possible to perform reoperation in only two patients with recurrence, both previously submitted to sphincter-saving surgery and diagnosed by transanal ultrasonography and biopsy. The high incidence of local recurrence in this series is explained by the advanced stage of disease in the majority of patients. Since the choice between APR and sphincter-saving resection does not seem to affect the incidence of local recurrence, which was related more to tumour size, site, stage and grading, preservation of the sphincters and restoration of intestinal continuity should be the aim whenever technically possible.

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References

1. Sakurai S, Shinagawa N, Fukui T, Yura J. Bacterial adherence to human gallbladder epithelium. *Surg Today* (*Jpn J Surg*) 1992; **22**: 504–7.
2. Yonemura Y, Ohoyama S, Kimura H *et al.* Independent clinical and flow cytometric prognostic survival of patients with stage I gastric cancer. *Surg Today* (*Jpn J Surg*) 1992; **22**: 416–20.
3. Matsui M, Kojima O, Kawakami S, Uehara Y, Takahashi T. The prognosis of patients with gastric cancer possessing sex hormone receptors. *Surg Today* (*Jpn J Surg*) 1992; **22**: 421–5.
4. Sakamoto J, Koike A, Saji S, Teramukai S, Ohashi Y, Nakazato H. Preoperative serum immunosuppressive acidic protein (IAP) test for the prognosis of gastric cancer: a statistical study of the threshold level and evaluation of the effect of the biological response modifier PSK. *Surg Today* (*Jpn J Surg*) 1992; **22**: 530–6.
5. Umehara Y, Kimura T, Yoshida M, Oba N, Harada Y. Metastatic node and DNA ploidy in gastric carcinoma. *Surg Today* (*Jpn J Surg*) 1992; **22**: 405–8.
6. Naito M, Iwafuchi M, Ohsawa Y *et al.* An experience of cell sorting using samples isolated from paraffin-embedded tissue of neuroblastoma. *Surg Today* (*Jpn J Surg*) 1992; **22**: 435–8.
7. Schutte B, Reynders MMJ, Bosman FT, Blijham GH. Flow cytometric determination of DNA ploidy level in nuclei isolated from paraffin-embedded tissue. *Cytometry* 1985; **6**: 26–30.
8. Arima S, Yoshimura S, Futami K, Yao T. The postoperative recurrence of Crohn's disease: an analysis of 37 patients with Crohn's disease who underwent endoscopy during initial surgery. *Surg Today* (*Jpn J Surg*) 1992; **22**: 346–50.
9. Tuscano D, Catarci M, Saputelli A *et al.* Low anterior resection *versus* abdominoperineal excision: a comparison of local recurrence after curative surgery for 'very low' rectal cancer. *Surg Today* (*Jpn J Surg*) 1992; **22**: 313–17.

Digest

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Dr Hiram Polk, Editor of The American Journal of Surgery, *has this month selected the best of October to December 1992 from that journal for his summary. A reciprocal digest written by our own Professor John Farndon appears in the American journal.*

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Pancreatic cancer

Surgeons have contributed greatly to the description of the alimentary tract as the largest endocrine organ within the body. Understanding the endocrine source or responsiveness of some gastrointestinal diseases has provided a new insight into their management. There is no better example than the study provided by the French Association for Surgical Research of the responsiveness of pancreatic cancer to gonadoliberin and somatostatin[1]. The laboratory data supporting the potential inhibition of such tissue growth is sound but the clinical application is disappointing. There was a significant improvement in 20 per cent of the patients and the tumours were often very extensive. This provides a focus for further studies and if patients were better stratified then results may be improved in future trials.

Surgical technique

The exposure of surgical sites at the junction of body compartments, i.e. diaphragm and pelvis, is generally unfamiliar, rarely needed and often not very well performed. Karakousis provides a well illustrated example of an approach to the iliac fossa, external iliac vessels and the bony wall of the pelvis[2]. Although rarely warranted, this seems to provide an uncommonly good exposure of a complex body compartment.

Anastomotic healing

Anastomotic failure in the intestine remains an Achilles' heel of the broad-based practice of surgery. Professor Goris and his group at Nijmegen in the Netherlands have identified an interesting predilection for greater collagen synthetic capacity in the small bowel than in the colon. A regional reaction was observed in that the synthetic capacity occurred throughout the small bowel and was partly specific for collagen[3].

Vascular trauma

Revascularization procedures, especially in the lower extremity, and the use of microsurgery are important techniques for the trauma surgeon in the management of distal vascular injury. Malone and associates[4] reported experience with 99 injuries distal to the brachial or popliteal trifurcations in 88 patients. Nerve and tendon injuries and fracture dislocations occurred often with the typically penetrating trauma. Fasciotomy was a useful adjunct in selected patients. When the vascular injury was isolated the results were excellent and reconstruction or ligation as chosen by the surgeon was effective. With multiple arterial injuries in the same extremity the surgeon's choice was more difficult. The authors found that the preservation of a single functional artery distal to the elbow or knee was sufficient for limb viability and function. Ligation of vessels, provided patency was maintained in at least one other, was a useful therapeutic measure. The authors reiterate the primacy of nerve injury in determining long-term functional loss in the extremity.

Breast cancer

Regional surgical societies in the USA contribute broadly to the value of all journals and the South-western Surgical Congress encompasses a large part of the United States and an area in which the growth of population has recently been substantial. There is a nationwide concern promulgated, if not created, by the lay media that surgeons have favoured radical approaches and been very slow to embrace more conservative methods of therapy in the treatment of breast cancer. Abernathy and associates at the Denver General Hospital asked whether these actions were based on the surgeon's advice or the patient's choice[5]. Based on the responses of 175 surgeons in Colorado to a questionnaire, they identified one surgeon in three who admitted to providing subtly biased information in favour of the more traditional modified radical mastectomy. This is surely a time-dependent phenomenon. The development of further data and longer follow-up of breast-conserving procedures should allow this proportion to reduce further. The considerable difference in costs for breast-conserving therapy is an important factor and, with the so-called 'healthcare reform movement' in the USA, data of this sort help dispel misunderstanding and identify those who need additional information in these areas.

Cardiac surgery

A San Antonio group examined the risk of major elective operation in patients who have undergone myocardial revascularization by coronary artery bypass grafting[6]. The popularity and broad use of the latter procedure have created a population that may require subsequent major surgery. Morbidity and mortality were studied in a well stratified collection of patients and no differences were identified. Surgeons can, therefore, safely approach the patient who has had a successful myocardial revascularization in an objective fashion knowing that if further surgery is warranted it can be performed safely. Overall symptoms and functional status need to be considered as before.

Prosthetic materials

The properties of prosthetic materials that permit repair of arteries, hernias and so forth have been studied in detail for some time. A report from a unit in Arizona which has long had an interest in basic wound healing identified an increase in thrombogenicity of polytetrafluoroethylene (PTFE) when certain manipulations were carried out[7]. They stressed that less than meticulous manipulation of PTFE with surgical

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instruments significantly impaired healing and is a possible causative factor in the poor long-term performance of some grafts.

Burns

A series of 547 elderly patients with burns was the focus of a study from the burn unit at Parkland Memorial Hospital in Dallas[8]. No patient over the age of 65 years and with burns of >47 per cent of body surface area survived. The currently popular early excision and grafting did not alter survival in patients with lesser burns, but the length of hospital stay was improved. Such data are helpful to the surgeon who faces the difficult moral issue of the extent of care in the older patient with burns.

Endocrine surgery

The Society of Head and Neck Surgeons provides important balance in an ever more specialty-oriented field for the practising general surgeon. Cancers of the thyroid provide perplexing data because of the favourable prognosis and long-term survival and the difficulty in identifying subtle differences in effects of treatment with such long delayed outcome. Auguste and associates[9] studied *HER-2/neu* oncogenes and cytoplasmic *myc*. There was no expression of the former in 21 follicular adenomas or 20 follicular carcinomas but the c-*myc* oncogene was expressed significantly more often in malignant lesions than in benign follicular neoplasm. This difference was not associated with a survival advantage.

Much of the management of follicular cancers of the thyroid is dependent on the accuracy of frozen-section examination of the ipsilateral total lobectomy specimen. Davis and associates[10] from the Vancouver General Hospital examined 198 patients who underwent frozen-section pathological examination at the time of operation. There were no false positives but 27 per cent false negatives. This is representative of practice across the USA and could not be improved by stratification of patients by age (>50 years), size of the nodule (>3 cm), or a positive history of prior neck irradiation. These data indicate that the informed patient coming to thyroidectomy and frozen-section evaluation needs to appreciate the possibility of error and potential further operation if warranted.

Maddox, Urist and associates at the University of Alabama recently re-examined their experience with cervical lymph node metastasis from well differentiated thyroid cancer[11]. The extent of node dissection has been widely debated in surgical practice and is a hostage to the extraordinarily favourable prognosis and anticipated long survival in the vast majority of such patients. The authors identified lymph node metastasis as the most important prognostic variable. The data did not permit evaluation of the extent of node dissection under different clinical circumstances. The best judgement of the surgeon and postoperative suppressive therapy seem to be the keystones of quality care.

The failed exploration of the patient with overt hyperparathyroidism is the most disconcerting area of practice in endocrine surgery. Silver and Velez examined 27 reoperations and found that 21 of 26 patients undergoing attempted localization were aided by such studies[12]. Invasive procedures such as selective vein catheterization and/or arteriography were effective in 12 of 15 patients and less invasive procedures including scintigraphy, magnetic resonance imaging, computed tomography and ultrasonography were accurate in 14 of 21. Twenty-three of the patients were cured by a second operation. The localization of parathyroid tissue continues to be a popular subject among surgical investigators and this report represents a high standard of performance in a difficult clinical situation.

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References

1. Huguier M, Samama G, Testart J *et al.* Treatment of adenocarcinoma of the pancreas with somatostatin and gonadoliberin (LH-RH). *Am J Surg* 1992; **164**: 384–53.
2. Karakousis CP. The abdominoinguinal incision in resection of pelvic tumors with lateral fixation. *Am J Surg* 1992; **164**: 366–71.
3. Martens MFWC, de Man BM, Hendriks T, Goris RJA. Collagen synthetic capacity throughout the uninjured and anastomosed intestinal wall. *Am J Surg* 1992; **164**: 354–60.
4. Ballard JL, Bunt TJ, Malone JM. Management of small artery vascular trauma. *Am J Surg* 1992; **164**: 316–19.
5. Tarbox BB, Rockwood JK, Abernathy CM. Are modified radical mastectomies done for T_1 breast cancers because of surgeon's advice or patient's choice? *Am J Surg* 1992; **164**: 417–22.
6. Nielsen JL, Page CP, Mann C, Schwesinger WH, Fountain RL, Grover FL. Risk of major elective operation after myocardial revascularization. *Am J Surg* 1992; **164**: 423–6.
7. Holubec H, Hunter GC, Putnam CW, Bull DA, Rappaport WD, Chvapil M. Effect of surgical manipulation of polytetrafluoroethylene grafts on microstructural properties and healing characteristics. *Am J Surg* 1992; **164**: 512–16.
8. Hunt JL, Purdue GF. The elderly burn patient. *Am J Surg* 1992; **164**: 472–6.
9. Auguste L-J, Masood S, Westerband A, Belluco C, Valderamma E, Attie J. Oncogene expression in follicular neoplasms of the thyroid. *Am J Surg* 1992; **164**: 592–3.
10. Kingston GW, Bugis SP, Davis N. The role of frozen section and clinical parameters in distinguishing benign from malignant follicular neoplasms of the thyroid. *Am J Surg* 1992; **164**: 603–5.
11. Sellers M, Beenken S, Blakenship A *et al.* Prognostic significance of cervical lymph node metastases in differentiated thyroid cancer. *Am J Surg* 1992; **164**: 578–81.
12. Silver CE, Velez FJ. Parathyroid reexploration. *Am J Surg* 1992; **164**: 606–9.

Eurosurgery/Eurochirurgie '92

The following 16 papers are based on presentations made at the Eurosurgery/Eurochirurgie '92 meeting held in Bruxelles, Belgium, on 2–5 June 1992 under the Presidency of Mr Adrian Marston.

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High incidence of arteriovenous fistula after biopsy of kidney allografts

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Arteriovenous fistula (AVF) is a well known but rarely diagnosed complication of percutaneous biopsy of kidney allografts. In the past diagnosis was usually made when clinical signs of an AVF occurred but Doppler ultrasonography has now enabled non-invasive diagnosis. Doppler examination of kidney allografts was performed after 100 biopsies. A total of ten AVFs were diagnosed within 2 weeks of biopsy. On repeated examination 2 months later, no additional fistula was detected. All fistulas were detected by abnormal colour shading of the artery and vein of the fistula caused by high blood velocity. Quantification in the artery supplying the fistula showed a higher systolic velocity compared with that in a normal artery of comparable size and location in the graft (mean (range) 64 (25–150) versus *36 (20–65) cm/s,* $P < 0·05$*). Diastolic velocity was also higher in the artery supplying the fistula than in a normal artery (mean (range) 34 (9–72)* versus *7 (0–13) cm/s,* $P < 0·05$*). In the group with an AVF the proportion with a prolonged bleeding time (>3 min) was higher (80* versus *47 per cent,* $P < 0·05$*), as was the prevalence of a platelet count <200 ×* 10^9*/l (60* versus *22 per cent,* $P < 0·05$*). After detection of the fistula, four of the grafts were lost because of rejection and two patients died from sepsis during antirejection treatment. During follow-up of the remaining four AVFs, three disappeared spontaneously and one persisted. None of the fistulas has had an impact on renal function requiring intervention. In conclusion, AVF is a complication observed frequently after kidney allograft biopsy that can be detected and monitored by Doppler ultrasonography.*

Arteriovenous fistula (AVF) is a well recognized complication after biopsy both in the native kidney[1,2] and in a kidney allograft. After renal transplantation, percutaneous biopsy is used routinely to establish a diagnosis of rejection. Case reports of AVF after biopsy from a kidney allograft have been published[3–9], but the incidence of this complication is not well known. Recently, incidences of 1–2 per cent after all allograft biopsies have been reported[10,11]. The detection of a fistula is possible using angiography[4,6,7,10,11] or radionuclide scanning[3] and several reports have been published recently on the applicability of Doppler ultrasonographic examination[5,9,12]. This non-invasive technique is particularly suitable for the detection of AVFs following kidney allograft biopsy, not only because images of the allograft can be obtained, but also because Doppler spectra can be used to describe changes in haemodynamics[13,14].

In this study Doppler examination was routine shortly after every kidney allograft biopsy to detect possible AVFs. Additionally, possible risk factors for the occurrence of a fistula were analysed and all fistulas detected were followed up.

Patients and methods

Doppler ultrasonography was performed in all patients undergoing transplantation between May 1990 and September 1991 who had a kidney allograft biopsy. Transplantation was carried out using standard surgical techniques with end-to-side anastomosis on the external iliac vessels. Biopsies were taken with a 14-G Tru-Cut needle (Travenol Laboratories, Deerfield, Illinois, USA) when the cause of renal dysfunction had to be established. Doppler examination was performed with a Toshiba SSA-270-A colour duplex scanner with a 3·75-MHz probe (Toshiba, Tokyo, Japan) within 2 weeks of biopsy. The probe was placed on the lateral region of the abdomen to visualize the position and anatomy of the kidney allograft. The colour-coded Doppler representation was used to identify the vessels of the allograft. Initial detection of an AVF is possible on the real-time Doppler image by random colour assignment caused by tissue vibration or by abnormal colour shading of the artery and vein of the fistula compared with the normal vessels of the graft[5]. Doppler spectra from a normal segmental artery and from the artery supplying the AVF were obtained. The systolic and diastolic velocities in these arteries were measured. The insonation angle of the Doppler beam was kept below 60°. The resistance index (RI) of the spectrum was calculated using the formula[15]:

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Table 1 *Doppler spectrum waveform characteristics of arteriovenous fistulas and comparable normal arteries in kidney allografts*

	Artery supplying fistula			Normal artery			
Patient no.	Systolic velocity (cm/s)	Diastolic velocity (cm/s)	RI	Systolic velocity (cm/s)	Diastolic velocity (cm/s)	RI	ΔRI
1	68	30	0·56	43	10	0·77	0·21
2	25	9	0·64	20	5	0·75	0·11
3	111	72	0·35	37	8	0·78	0·43
4	60	35	0·42	65	13	0·80	0·38
5	70	48	0·31	32	4	0·88	0·57
6	31	16	0·48	33	7	0·79	0·31
7	27	14	0·48	42	0	1·00	0·52
8	150	66	0·56	32	10	0·69	0·13
9	25	13	0·48	20	0	1·00	0·52
10	74	32	0·57	40	10	0·75	0·18

Measurements were made 2–14 days after biopsy. RI, resistance index

$$\mathrm{RI} = \frac{\text{systolic velocity}-\text{diastolic velocity}}{\text{systolic velocity}}$$

The RI is a parameter that characterizes the peripheral resistance of an artery[13–15]. The venous flow pattern in the allograft was also assessed for features of arterialization; these can be seen in veins draining a fistula. Clinical data at the time of biopsy were recorded to assess whether risk factors for the occurrence of a fistula could be identified. Serum creatinine concentration and haematological characteristics were determined using standard laboratory techniques. In all patients Doppler ultrasonography was repeated after 2 months to detect fistulas that might have been too small for identification previously but that had later increased in size. Also, all fistulas detected were followed up to assess changes with time.

Statistical analysis was performed using Student's t test or Kruskal–Wallis analysis for two groups where appropriate. $P < 0{\cdot}05$ was considered significant.

Results

During the observation period 100 biopsies were performed in 62 patients. A biopsy was taken at 1–52 (median 4) weeks after transplantation. Doppler ultrasonography was performed 1–14 (median 2) days after biopsy. These initial examinations disclosed ten AVFs (incidence 10 per cent). Most fistulas were detected on an initial overview of the sonographic image. In one case the difference in RI between segmental arteries and arterialization of the venous signal prompted the investigator to search for a fistula, which was then identified. The presence of a fistula was confirmed during follow-up when it had increased in size and showed the same characteristics as the other fistulas. Doppler waveform characteristics of the fistulas detected are shown in *Table 1*. The mean (range) systolic velocity was higher in arteries supplying the AVF than in normal arteries (64 (25–150) *versus* 36 (20–65) cm/s, $P < 0{\cdot}05$). The diastolic velocity was also higher in the former (mean (range) 34 (9–72) *versus* 7 (0–13) cm/s, $P < 0{\cdot}05$). This resulted in a lower RI for the artery supplying the AVF compared with that of a normal artery (mean (range) 0·48 (0·31–0·64) *versus* 0·82 (0·69–1·00), $P < 0{\cdot}05$).

Haematuria occurred for several days after biopsy in two of the ten patients (20 per cent) with an AVF, but in only six of the 90 (7 per cent) in whom no fistula was observed. A bruit over the area of the allograft was heard in four of the ten patients with a fistula but in none of the others. Rejection was diagnosed in 50 per cent of the biopsies causing an AVF and in 69 per cent of the others; the difference was not significant. In four of the ten biopsies that had caused a fistula, parts of the arterial wall were seen in the biopsy. Clinical data for the patients at the time of biopsy are shown in *Table 2*. There were significant differences between groups without and with an AVF in the proportion of patients who had a bleeding time >3 min (47 *versus* 80 per cent) and a platelet count <200 × 10^9/l (22 *versus* 60 per cent).

Table 2 *Clinical data for patients with and without arteriovenous fistula after kidney allograft biopsy*

	No fistula (n = 90)	With fistula (n = 10)	P
Systolic blood pressure (mmHg)*	158(27)	148(30)	n.s.
Diastolic blood pressure (mmHg)*	89(14)	82(13)	n.s.
Serum creatinine (μmol/l)*	407(237)	430(237)	n.s.
Activated partial thromboplastin time (s)*	32(5)	34(8)	n.s.
Ivy bleeding time >3 min†‡	42 (47)	8 (80)	<0·05
Platelet count <200 × 10^9/l†	20 (22)	6 (60)	<0·05
International ratio >1·2†	5 (6)	2 (20)	n.s.
Cyclosporin immunosuppression†	55 (61)	5 (50)	n.s.

* Values are mean(s.d.); † values in parentheses are percentages. ‡ Mean of three consecutive measurements. n.s., Not significant

Doppler ultrasonography was repeated in all patients 7–10 (median 8) weeks after biopsy to detect any fistula that might have become visible only after an increase in size with time, and to detect any spontaneous closure of an already established AVF. No new fistula was found and none of the lesions detected earlier had spontaneously disappeared at that time.

During follow-up, two patients died from sepsis after antirejection treatment. In four others the graft was lost to rejection within 2 weeks of biopsy. In the remaining four patients the AVFs were followed for between 15 and 24 weeks after biopsy. Doppler examination showed that three of these fistulas had disappeared spontaneously, whereas the remaining fistula showed increased blood velocities. However, the patient affected has suffered neither deterioration of renal function nor any complaint that could be attributed to the fistula up to 18 months after biopsy.

Discussion

The Doppler characteristics of AVFs after renal allograft biopsy have been described earlier[5,9,12] and the present findings are in concordance with these data. The RI, a measure of peripheral resistance of an artery, was considerably lower in all fistulas compared with the index of a normal artery in the allograft. In this study, however, the velocities in the normal artery and the AVF during the first examination after biopsy showed more overlap than in the descriptive study of Middleton *et al.*[5]. This may be because the first examinations in the present study were made shortly after biopsy when the fistulas were still relatively small, resulting in lower blood velocities in the supplying artery. Furthermore, examination was performed on a routine basis whereas a selected group of patients was investigated in other studies[5,10].

The incidence of AVF in the present series was 10 per cent. This is rather high compared with the values of 1 and 2 per cent reported in previous studies[10,11] where clinical symptoms were the indication for performing angiography that disclosed the fistula. Duplex examination was routine after biopsy in the present study, so more AVFs were detected. The incidence in this series is more in agreement with the values of 15–18 per cent found by routine angiography performed after biopsy of native kidneys[1,2].

Parts of the arterial wall were found in four of the ten biopsies that had caused an AVF. Because not all of the biopsy material was always examined, no definitive conclusion can be drawn from this observation. In agreement with the findings of Lawen *et al.*[10], no association could be made between the presence of signs of rejection in the biopsy and the occurrence of an AVF. However, the clinical data taken at the time of biopsy showed significantly higher percentages of patients with a prolonged bleeding time and a low platelet count in those with a fistula than in the other group. It seems that, together with the circumstantial factor of arterial damage from the biopsy needle, the haemostatic condition of the patient contributes to the risk of developing a fistula. The occurrence of a fistula is probably a multifactorial event, to which haemostatic factors and factors associated with the biopsy technique both contribute. Contrary to the findings of others[10], cyclosporin immunosuppression did not seem to be associated with an increased risk of AVF development.

The present study suggests that the consequences of an AVF are limited. In most cases the fistula never became clinically significant, because the graft was lost to rejection or the patient died. Most of the remaining fistulas disappeared spontaneously. Spontaneous disappearance has also been reported elsewhere[16]. A persisting fistula, as observed in one patient in the present series, may exist without renal dysfunction or signs of hyperdynamic circulation[4,5,10]. However, others have reported deterioration of renal function and uncontrollable hypertension resulting from a fistula; these are features that may require correction either surgically or by percutaneous embolization[6,7,9–12]. According to Lawen *et al.*[10] most AVFs were found in patients who had undergone biopsy more than 1 year after transplantation and most of these needed correction. This discrepancy with the present study may be because most of the biopsies in this series were taken approximately 4 weeks after transplantation and many grafts were lost before the fistula could develop to an extent where it was a threat to renal function. Lawen *et al.*[10] found that AVFs were detected in 0·6 per cent of biopsies taken in the first year after transplantation. After biopsy taken beyond the first year, the proportion was 3·5 per cent. They attributed this higher incidence to the histological features of the graft after 1 year: arterial wall thickening and intimal fibrosis. In our opinion, it may equally well have been caused by the higher loss of grafts in the first year, preventing some of the fistulas reaching the level of clinical significance.

In conclusion, Doppler ultrasonography provides an easy, non-invasive method for detecting and monitoring AVFs after kidney allograft biopsy. In this prospective study the incidence of fistula was 10 per cent of all biopsies. Haemostatic factors seem to contribute to the occurrence of a fistula. None of these early detected fistulas caused deterioration of renal function requiring intervention.

Acknowledgements

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References

1. Bennett AR, Wiener SN. Intrarenal arteriovenous fistula and aneurysm: a complication of percutaneous renal biopsy. *AJR Am J Roentgenol* 1965; **95**: 372–8.
2. Ekelund L, Limdholm T. Arteriovenous fistulae following percutaneous renal biopsy. *Acta Radiol* 1971; **11**: 38–48.
3. Cooper PH, Maisey MN, Shaw P. Arteriovenous fistula following renal transplant biopsy. *Br J Radiol* 1984; **57**: 181–3.
4. Debruyne FMJ, Koene RAP, Moonen WA, Renders GAM, Chafik ML. Intrarenal arteriovenous fistula following renal allograft biopsy. *Eur Urol* 1978; **4**: 435–7.
5. Middleton WD, Kellman GM, Melson GL, Madrazo BL. Postbiopsy renal transplant arteriovenous fistulas: color Doppler US characteristics. *Radiology* 1989; **171**: 253–7.
6. Morse SS, Sniderman KW, Strauss EB, Bia MJ. Postbiopsy renal allograft arteriovenous fistula: therapeutic embolization. *Urol Radiol* 1985; **7**: 161–4.
7. Schmid T, Sandbichler P, Ausserwinkler M, Pernthaler H, Margreiter R. Vascular lesions after percutaneous biopsies of renal allografts. *Transpl Int* 1989; **2**: 56–8.
8. Sennett CA, Messersmith RN, Yousefzadeh DK, Thistlethwaite JR Jr. Percapsular and percutaneous embolization of renal transplant pseudoaneurysm and AV-fistula: case report. *Cardiovasc Intervent Radiol* 1989; **12**: 270–3.
9. Taylor KJW, Morse SS, Rigsby CM, Bia M, Schiff M. Vascular complication in renal allografts: detection with duplex Doppler US. *Radiology* 1987; **162**: 31–8.
10. Lawen JD, van Buren CT, Lewis RM, Kahan BD. Arteriovenous fistulas after renal allograft biopsy: a serious complication in patients beyond one year. *Clin Transpl* 1990; **4**: 357–69.
11. Thistlethwaite JR Jr, Woodle ES, Mayes JT *et al.* Aggressive needle biopsy protocol prevents loss of renal allografts to undetected rejection during early posttransplant dysfunction. *Transplant Proc* 1989; **21**: 1890–2.
12. Renowden SA, Blethyn J, Cochlin DL. Duplex and colour flow sonography in the diagnosis of post-biopsy arteriovenous fistulae in the transplanted kidney. *Clin Radiol* 1992; **45**: 233–7.
13. van Asten WNJC, Beijneveld WJ, Pieters BR, van Lier HJJ, Wijn PFF, Skotnicki SH. Assessment of aortoiliac obstructive disease by Doppler spectrum analysis of blood flow velocities in the common femoral artery at rest and during reactive hyperemia. *Surgery* 1991; **109**: 633–9.
14. Merkus JWS, van Asten WNJC, Hoitsma AJ, Koene RAP, Skotnicki SH. Assessment of hemodynamic changes in human kidney grafts induced by cyclosporin infusion. *Transpl Int* 1991; **4**: 136–9.
15. Planiol T, Pourcelot L. Doppler effect study of the carotid circulation. In: White D, McCready V, Vlieger M, eds. *Ultrasonics in Medicine.* Amsterdam: Excerpta Medica, 1974: 104–11.
16. Herschman A, Klein MJ, Blumberg AG. Spontaneous disappearance of iatrogenic renal arteriovenous fistula: report of a case. *J Urol* 1971; **105**: 4–6.

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Autologous predonation, haemodilution and intraoperative blood salvage in elective abdominal aortic aneurysm repair

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The feasibility of predonated autologous blood transfusion and intraoperative blood salvage in elective abdominal aortic aneurysm repair was studied. Twenty consecutive patients were evaluated, of whom five were excluded according to protocol criteria. Patients each donated 1 unit blood 14 and 7 days before operation. A third unit was withdrawn in the anaesthetic room and replaced with Hartmann's solution, producing a haemodiluted state. Intraoperative losses were minimized using the Haemonetics Cell Saver III Plus autotransfusion system. Predonated blood from two patients passed its expiry date owing to repeated operation postponements, leaving 13 patients for study. The mean(s.d.) intraoperative blood loss was 700(300) ml with a mean(s.d.) intraoperative salvage of 420(300) ml. Two patients were transfused with bank blood in breach of the protocol and two others were transfused according to clinical need. Thus nine patients safely avoided homologous transfusion. With autologous predonation, haemodilution and intraoperative blood salvage, elective aortic aneurysm repair can be performed safely with minimal need for homologous blood.

Abdominal aortic aneurysm (AAA) affects 1–4 per cent of the population over 50 years and causes 1·3 per cent of all male deaths over the age of 65 years[1]. Greater longevity, improved detection and better community awareness of the disease through aneurysm screening programmes are likely to lead to increasing numbers of patients undergoing elective AAA repair. Each operation places demands on the blood transfusion service and each unit transfused exposes the patient to the risk of disease transmission and incompatibility.

Infections transmitted by homologous blood transfusion include hepatitis[2], acquired immune deficiency syndrome[3] and cytomegalovirus[2,4]. Sensitization to red cell, white cell and platelet antigens in donor blood leads to febrile reactions in up to 5 per cent of all transfusions[5,6]. The potential risks of ABO and rhesus incompatibility are minimized by the rigorous cross-matching procedure. The use of autologous blood transfusion virtually abolishes the risk of disease transmission and incompatibility while conserving valuable stores of bank blood for emergency use.

Predonation[7–10], haemodilution[11,12] and intraoperative blood salvage[13–17] are established techniques for conserving bank blood in surgery. The aim of this study was to minimize homologous blood requirements in elective AAA surgery by combining these three techniques.

Patients and methods

Twenty consecutive patients undergoing elective AAA repair were considered for study. Patients were excluded according to the criteria listed in *Table 1*, which are modifications of the guidelines for autologous transfusion set out by the British Society for Haematology and the British Blood Transfusion Society[18].

Eligible patients donated 1 unit (450 ml) blood 14 days before the scheduled surgery date and again 7 days later. Each unit collected was stored separately from the routine blood stocks. Collected into standard bags containing citrate phosphate–dextrose with adenine, the predonated blood had a storage life of 35 days; this allowed a 3-week period during which the date of surgery could be postponed, if necessary. Time-expired predonated blood was discarded.

Haemoglobin levels were measured immediately before each donation and on the day before surgery. A level <10 g/dl at any time before operation required that the patient was withdrawn from the study. Patients were given 200 mg ferrous sulphate orally three times a day throughout the preoperative period and for 6 weeks after operation to prevent iron deficiency[7]. On the day before surgery, blood was taken for cross-matching and final checking against the previously donated blood.

In the anaesthetic room before induction, 450 ml blood was withdrawn and replaced with 500 ml Hartmann's solution to provide a third unit of autologous blood and to induce a state of normovolaemic haemodilution. For the operation, a standard anaesthetic technique combining epidural and general anaesthesia was used. Surgery was performed via the transperitoneal route and each patient was given a bolus of 5000 units heparin intravenously before aortic cross-clamping. The aneurysmal aortas were replaced with Gelsoft impregnated Dacron grafts (Vascutek, Inchinnan, UK) using a standard inlay technique.

Intraoperative blood lost was salvaged using the Cell Saver III Plus autotransfusion system (Haemonetics, Leeds, UK). This processes blood aspirated from the operative site to provide packed red cells for retransfusion. The fresh unit of autologous blood collected in the anaesthetic room was returned to the patient before clamp release on completion of the graft, followed by salvaged intraoperative losses and predonated autologous units as required. Any residual autologous units were transfused after operation. Thereafter, patients were given homologous bank blood if the haemoglobin level fell to <9·0 g/dl, although a final decision regarding transfusion was made on clinical grounds. Each patient gave written informed consent to participate in the study and the protocol was approved by the hospital research ethics committee.

Table 1 *Exclusion criteria for autologous predonation*

- Significant cardiovascular or cerebrovascular disease
  - Angina pectoris
  - Hypertension treated with β-blockers or angiotensin-converting enzyme inhibitors
  - Previous CVA
  - History of TIA, CVA or myocardial infarction in the preceding 12 months
- Haemoglobin level <12 g/dl in men or <11 g/dl in women
- Active bacterial infection
- Epilepsy

TIA, transient ischaemic attack; CVA, cerebrovascular accident

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Results

Of the 20 patients, two were excluded because of concurrent angina, two because of β-blocker therapy for hypertension and one owing to a previous minor stroke. Thus 15 patients predonated blood. Two more were subsequently excluded because their predonated blood exceeded its storage life and was discarded following repeated operation postponement. This left 13 patients managed according to the protocol. All had infrarenal aneurysms, ranging in diameter from 5·2 to 9·0 cm. One required a bifurcated prosthesis while the remaining 12 received straight grafts.

No problems were encountered with predonation apart from one mild vasovagal episode. Some 2 units blood were predonated in the weeks before surgery by all but one patient, in whom venepuncture was difficult and only 1 unit was obtained. Withdrawal of the third unit in the anaesthetic room was omitted in three cases because of unfamiliarity of staff with the protocol. There were thus four patients who had only 2 units predeposited autologous blood in reserve, while the remainder had 3.

The mean(s.d.) intraoperative blood loss was estimated at 700(300) ml by adding salvaged blood volume to that lost into swabs and drapes. The mean(s.d.) volume of salvaged blood retransfused was 420(300) ml, or 60 per cent of the estimated intraoperative blood loss.

Haemoglobin levels in all patients fell in response to predonation, despite iron therapy. There was a further fall over the period of surgery, with lowest levels being reached from the first to third day after operation. Levels had generally risen by the seventh day and all had returned towards the original preoperative level after 6 weeks. Changes in haemoglobin level of the 13 patients completing the protocol are shown in *Figure 1*. In two cases sharp rises in haemoglobin were seen in the early postoperative period. These reflect the effects of blood transfusion.

Figure 2 summarizes the blood requirements of the 13 patients. Four were given homologous bank blood. Patients 1 and 3 were given bank blood early in the series because of unfamiliarity of staff with the study protocol. Patients 7 and 13 were transfused with bank blood on clinical grounds. Patient 7 did not receive any salvaged blood during operation but was given 4 units bank blood after surgery in addition to 3 units predeposited blood. Patient 13 was given 2 units bank blood on the second day after operation for clinically significant anaemia, with a haemoglobin level of 8·1 g/dl.

Postoperative complications comprised two cases of pulmonary atelectasis and one death. The latter occurred on the third day after operation from myocardial infarction. The length of hospital stay after operation ranged from 6 to 13 (median 8) days.

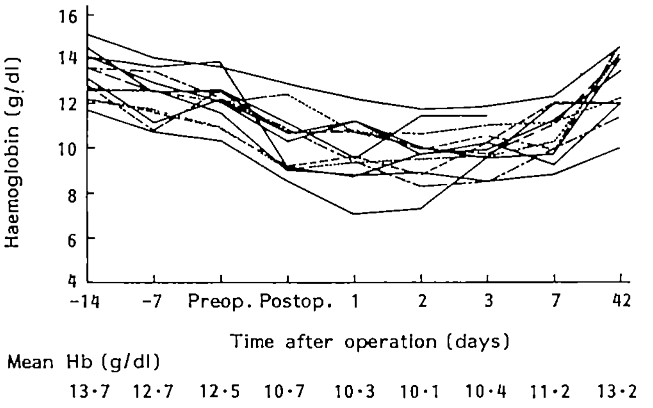

Figure 1 *Haemoglobin (Hb) levels over the study period for the 13 patients who completed the protocol*

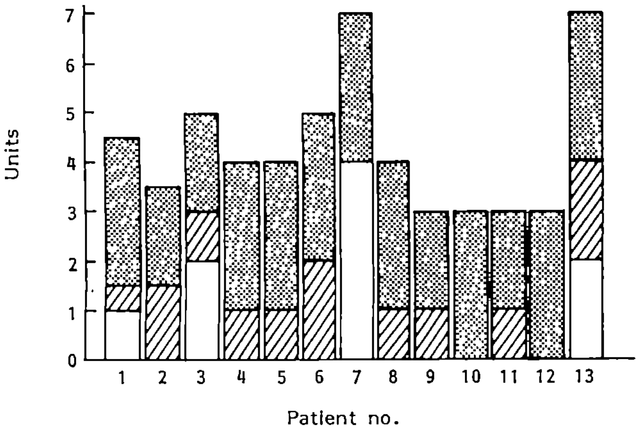

Figure 2 *Blood requirements for the 13 patients who underwent autologous transfusion. Patients 1, 3, 7 and 13 were given homologous bank blood.* ▨, *Predeposited blood (including predonated units and that withdrawn in association with haemodilution);* ■, *salvaged blood;* □, *bank blood*

Discussion

Predonation, haemodilution and salvage autotransfusion have each been shown to reduce transfusion needs; the potential savings of banked blood are great if they are used in combination. The technique of predonation is well established and several successful schemes have been reported[8–10]. However, predonation schemes can be used only for elective cases because of the time required for preoperative blood collection and only when the operation carries a high likelihood of transfusion[19]. Although some delays in the scheduled surgery can be absorbed, prolonged postponement will lead to blood expiry and wastage. This occurred in two of the present cases because of unavailability of intensive therapy unit beds. A high degree of coordination is therefore required between haematology, surgery, anaesthetic and intensive therapy staff to run a successful predonation scheme.

The use of autologous predonation does not entirely eliminate the risk of transfusion incompatibility. Careful attention must be paid to labelling and identification of blood and patients. Although a full cross-match is not necessary for autologous blood, some compatibility testing is recommended as a safeguard[20]. In this study ABO and rhesus checks were carried out on all patients and autologous blood units, as well as matching each unit against the patient using a Coombs' test.

Haemodilution has been used in a number of surgical specialties to reduce intraoperative red cell loss[11,12]. Anaemia is the major contraindication and the technique should be employed cautiously in patients with cardiac or renal disease. Although coagulation proteins and platelets are also diluted, clinical problems with haemostasis have not been encountered[10,20] and no adverse changes have been documented in pulmonary function or oxygen delivery at haematocrit values as low as 20 per cent[11].

The safety and efficacy of intraoperative blood salvage has been clearly established[15,21,22]. Although some morphological cellular disruption and an increase in free plasma haemoglobin does occur[13], researchers agree that prothrombin time, fibrinogen degradation products and D-dimer levels, renal function and clinical outcome are not adversely influenced[13–15]. While all surgeons would aim to minimize intraoperative bleeding by meticulous technique, there is inevitable blood loss from backbleeding vessels and 'flushing' of grafts that usually provides adequate blood for the salvage process to be worthwhile.

In this study, an autologous 'bank' of 3–5 units was available from predonation and intraoperative salvage to cover the AAA repair. Both the administration of erythropoietin during the period of predonation[23] and the 'piggyback' regimen, in which the oldest unit is retransfused into the patient while 2 more are withdrawn at a predonation session[24], may increase the amount of autologous blood that is available for operation but neither of these methods was used in the present study. Haemoglobin levels fell during the period of preoperative donation and remained steady at low levels for the first 3 days after operation. The rise observed over the following 4 days was considered to reflect a contraction of the intravascular space on removal of the epidural catheter. Although a haemoglobin level of 9·0 g/dl was used as the critical concentration for transfusion, others have suggested that a level of 8·0 g/dl is adequate and should not be associated with increased morbidity[25].

Nine of the 13 patients underwent successful AAA repair without homologous transfusion by combining autologous predonation, haemodilution and intraoperative blood salvage. In addition, there were two from the excluded group who did not require homologous blood, using only haemodilution and intraoperative salvage. Thus 11 of 20 patients avoided homologous transfusion altogether. As a result of this study, the routine cross-match order for AAA surgery in patients completing the predonation programme has been lowered from 6 to 2 units. It is expected that continued use of these techniques will help conserve valuable stores of bank blood as well as reducing the risks of disease transmission and incompatibility.

References

1. *Review of the Registrar General on Deaths by Cause, Sex and Age in England and Wales*. DH2 No. 10. London: HMSO, 1983.
2. Bove JR. Transfusion-associated hepatitis and AIDS. What is the risk? *N Engl J Med* 1987; **317**: 242–4.
3. Curran JW, Lawrence DN, Jaffe H, Kaplan J, Zyla LD, Chamberland M. Acquired immunodeficiency syndrome associated with transfusion. *N Engl J Med* 1984; **310**: 69–75.
4. Kay LA. The need for autologous blood transfusion. *BMJ* 1987; **294**: 137–9.
5. Rush B, Lee NLY. Clinical presentation of non-haemolytic transfusion reactions. *Anaesth Intensive Care* 1980; **8**: 125–31.
6. Goodnough LT, Schuck JM. Risks, options and informed consent for blood transfusion in elective surgery. *Am J Surg* 1990; **159**: 602–9.
7. Stehling L. Predeposit autologous blood donation. *Acta Anaesthesiol Scand Suppl* 1988; **89**: 58–62.
8. Herbert WN, Owen HG, Collins ML. Autologous blood salvage in obstetrics. *Obstet Gynecol* 1988; **72**: 166–70.
9. Macfarlane BJ, Marx L, Anquist K, Pineo G, Chenger J, Lassol E. Analysis of a protocol for an autologous blood transfusion program for total joint replacement surgery. *Can J Surg* 1988; **31**: 126–9.
10. Britton LW, Eastlund DT, Dzuiban SW *et al.* Predonated autologous blood use in elective cardiac surgery. *Ann Thorac Surg* 1989; **47**: 529–32.
11. Stehling L, Zauder HL. Acute normovolaemic haemodilution. *Transfusion* 1991; **31**: 857–68.
12. Messmer K. Hemodilution – possibilities and safety aspects. *Acta Anaesthesiol Scand Suppl* 1988; **89**: 49–53.
13. Clifford PC, Kruger AR, Smith A, Chant ADB, Webster JHH. Salvage auto-transfusion in aortic surgery: initial studies using a disposable reservoir. *Br J Surg* 1987; **74**: 755–7.
14. Duchateau J, Nevelsteen A, Demeyere R *et al.* Autotransfusion during aorto-iliac surgery. *Eur J Vasc Surg* 1990; **4**: 349–54.
15. Thompson JF, Webster JHH, Chant ADB. Prospective randomised evaluation of a new cell saving device in elective aortic reconstruction. *Eur J Vasc Surg* 1990; **4**: 507–12.
16. Imhoff M, Schmidtt R, Horsch S. Intra-operative autotransfusion with a new disposable system. *Ann Vasc Surg* 1986; **1**: 131–3.
17. Brener BJ, Rainer JK, Darling RC. Intra-operative autotransfusion in abdominal aortic resection. *Arch Surg* 1973; **107**: 78–84.
18. British Society for Haematology and British Blood Transfusion Society. Guidelines for autologous transfusion. *Clin Lab Haematol* 1988; **10**: 193–201.
19. Jaffray B, King P, Basheer MM, Gillon J. The efficiency of blood use and prospects for autologous transfusion in general surgery. *Ann R Coll Surg Engl* 1991; **73**: 235–8.
20. Rosberg B. Blood coagulation during and after normovolaemic hemodilution in elective surgery. *Annals of Clinical Research* 1981; **13**(Suppl 33): 84–8.
21. Lee D, Napier JAF. Autologous transfusion. *BMJ* 1990; **300**: 737–9.
22. Chant ADB, Thompson JF. Autologous transfusion with salvaged blood. *Br J Surg* 1992; **79**: 389–90.
23. Goodnough LT, Rudnick S, Price TH *et al.* Increased preoperative collection of autologous blood with recombinant human erythropoietin therapy. *N Engl J Med* 1989; **321**: 1163–8.
24. Matthey F. Autologous blood transfusion: indications and potential use in the UK. *Br J Hosp Med* 1988; **39**: 418–22.
25. Carson JL, Spence RK, Poses RM, Bonavita G. Severity of anaemia and operative mortality and morbidity. *Lancet* 1988; **i**: 727–9.

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References

1. *Review of the Registrar General on Deaths by Cause, Sex and Age in England and Wales*. DH2 No. 10. London: HMSO, 1983.
2. Bove JR. Transfusion-associated hepatitis and AIDS. What is the risk? *N Engl J Med* 1987; **317**: 242–4.
3. Curran JW, Lawrence DN, Jaffe H, Kaplan J, Zyla LD, Chamberland M. Acquired immunodeficiency syndrome associated with transfusion. *N Engl J Med* 1984; **310**: 69–75.
4. Kay LA. The need for autologous blood transfusion. *BMJ* 1987; **294**: 137–9.
5. Rush B, Lee NLY. Clinical presentation of non-haemolytic transfusion reactions. *Anaesth Intensive Care* 1980; **8**: 125–31.
6. Goodnough LT, Schuck JM. Risks, options and informed consent for blood transfusion in elective surgery. *Am J Surg* 1990; **159**: 602–9.
7. Stehling L. Predeposit autologous blood donation. *Acta Anaesthesiol Scand Suppl* 1988; **89**: 58–62.
8. Herbert WN, Owen HG, Collins ML. Autologous blood salvage in obstetrics. *Obstet Gynecol* 1988; **72**: 166–70.
9. Macfarlane BJ, Marx L, Anquist K, Pineo G, Chenger J, Lassol E. Analysis of a protocol for an autologous blood transfusion program for total joint replacement surgery. *Can J Surg* 1988; **31**: 126–9.
10. Britton LW, Eastlund DT, Dzuiban SW *et al.* Predonated autologous blood use in elective cardiac surgery. *Ann Thorac Surg* 1989; **47**: 529–32.
11. Stehling L, Zauder HL. Acute normovolaemic haemodilution. *Transfusion* 1991; **31**: 857–68.
12. Messmer K. Hemodilution – possibilities and safety aspects. *Acta Anaesthesiol Scand Suppl* 1988; **89**: 49–53.
13. Clifford PC, Kruger AR, Smith A, Chant ADB, Webster JHH. Salvage auto-transfusion in aortic surgery: initial studies using a disposable reservoir. *Br J Surg* 1987; **74**: 755–7.
14. Duchateau J, Nevelsteen A, Demeyere R *et al.* Autotransfusion during aorto-iliac surgery. *Eur J Vasc Surg* 1990; **4**: 349–54.
15. Thompson JF, Webster JHH, Chant ADB. Prospective randomised evaluation of a new cell saving device in elective aortic reconstruction. *Eur J Vasc Surg* 1990; **4**: 507–12.
16. Imhoff M, Schmidtt R, Horsch S. Intra-operative autotransfusion with a new disposable system. *Ann Vasc Surg* 1986; **1**: 131–3.
17. Brener BJ, Rainer JK, Darling RC. Intra-operative autotransfusion in abdominal aortic resection. *Arch Surg* 1973; **107**: 78–84.
18. British Society for Haematology and British Blood Transfusion Society. Guidelines for autologous transfusion. *Clin Lab Haematol* 1988; **10**: 193–201.
19. Jaffray B, King P, Basheer MM, Gillon J. The efficiency of blood use and prospects for autologous transfusion in general surgery. *Ann R Coll Surg Engl* 1991; **73**: 235–8.
20. Rosberg B. Blood coagulation during and after normovolaemic hemodilution in elective surgery. *Annals of Clinical Research* 1981; **13**(Suppl 33): 84–8.
21. Lee D, Napier JAF. Autologous transfusion. *BMJ* 1990; **300**: 737–9.
22. Chant ADB, Thompson JF. Autologous transfusion with salvaged blood. *Br J Surg* 1992; **79**: 389–90.
23. Goodnough LT, Rudnick S, Price TH *et al.* Increased preoperative collection of autologous blood with recombinant human erythropoietin therapy. *N Engl J Med* 1989; **321**: 1163–8.
24. Matthey F. Autologous blood transfusion: indications and potential use in the UK. *Br J Hosp Med* 1988; **39**: 418–22.
25. Carson JL, Spence RK, Poses RM, Bonavita G. Severity of anaemia and operative mortality and morbidity. *Lancet* 1988; **i**: 727–9.

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Intra-abdominal ectopic thyroid

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Ectopic thyroid tissue can be detected anywhere from the foramen caecum to the porta hepatis[1,2]. Most frequently it presents as a thyroglossal duct cyst associated with a normal thyroid gland. Less common is total ectopia, which can occur as a lingual thyroid or occasionally elsewhere in the body[1]. Suprahyoid, infrahyoid, intratracheal, intralaryngeal, intra-oesophageal, mediastinal, aortic, pericardial or cardiac ectopic thyroid tissue localizations are rarely seen. Ectopic thyroid tissue below the diaphragm is an extremely rare condition[3], seen mostly as struma ovarii. In this report a case of intra-abdominal thyroid gland is presented.

Case report

A 63-year-old woman was admitted with symptoms of anorexia, weakness, weight loss (7 kg in 3 months), dysphagia, vomiting and postprandial pain. Clinical examination and laboratory tests showed no abnormality except for a raised erythrocyte sedimentation rate (100 mm/h). On barium studies, a possible tumour mass was partially obstructing the cardio-oesophageal junction. Gastric cancer was suspected, and the patient underwent distal oesophagectomy, total gastrectomy, omentectomy, splenectomy and resection of the pancreatic tail. During operation, a lobular mass 10 × 7·5 × 5 cm was detected posterior to the spleen and stomach.

Microscopic examination of the diffuse infiltrating tumour of the stomach revealed an undifferentiated signet-ring cell carcinoma. In addition, behind the stomach and spleen lay the encapsulated tumour mass, the cut section of which was lobulated and of colloid appearance similar to thyroid tissue. Microscopic examination showed a multilobular structure composed of follicles that were lined with cuboidal epithelium and contained an acidophilic material (*Figure 1*). With alcian blue and mucicarmine stains no mucinous substance was observed. However, the epithelial cells reacted strongly with thyroglobulin (*Figure 2*) and a histopathological diagnosis of ectopic thyroid tissue with adenomatous hyperplasia was therefore made.

To seek further ectopic thyroid tissue, thyroid scintigraphy and whole-body scanning with ^{131}I were performed. No other thyroid tissue was detected. Levels of circulating hormones (T_3, T_4 and thyroid-stimulating hormone), thyroglobulin microsomal antibodies and thyroglobulin antibody were all normal.

Discussion

An ectopic thyroid gland is seen most often in the neck, less frequently in the chest and rarely in the abdomen. Intra-abdominal thyroid tissue is detected mostly as struma ovarii within ovarian teratomas in association with other fetal tissue remnants[3]. Otherwise, intra-abdominal thyroid tissue has been reported only as cell rests. Although Ramos-Gabatin and Pretorius[2] have proposed that ectopic thyroid tissue may occur anywhere from the foramen caecum to the porta hepatis along the embryological migration path, the present case is unique in that there was a distinct mass below the diaphragm containing thyroid tissue only.

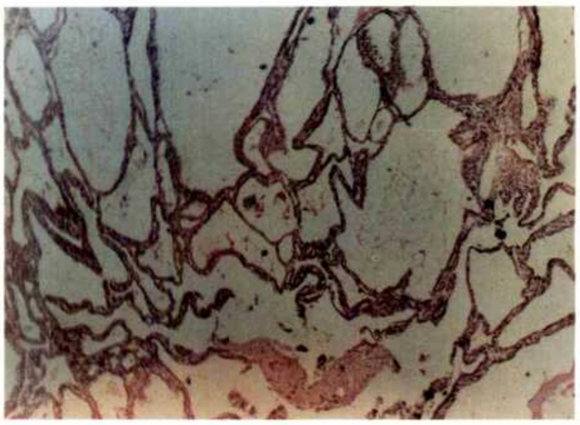

Figure 1 *Ectopic thyroid tissue. (Haematoxylin and eosin stain, original magnification × 32)*

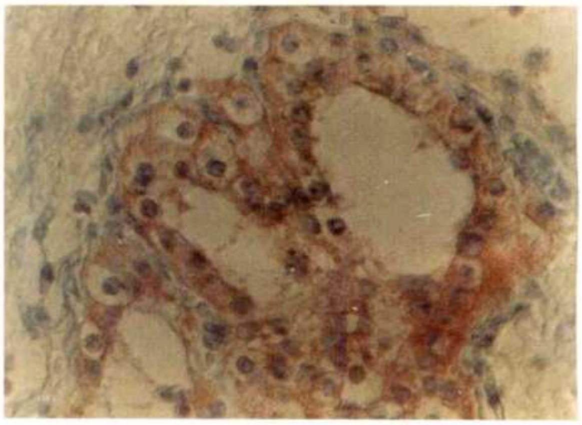

Figure 2 *Ectopic thyroid tissue. (Thyroglobulin stain, original magnification × 500)*

Takahashi *et al.*[4] found thyroid cells in the duodenal submucosa of a patient who had undergone pancreatoduodenectomy. In this case, follicular islands were detected but no gland formation was present, and the authors regarded this as metaplasia. In the present patient the ectopic thyroid tissue was separate from the coincidental gastric carcinoma and the orthotopic thyroid gland appeared to function normally.

References

1. Zink A, Rame F, Ziegler R. Papillary carcinoma in an ectopic thyroid. *Horm Res* 1991; **35**: 86–8.
2. Ramos-Gabatin A, Pretorius HT. Radionuclide turnover studies on ectopic thyroid glands – case report and survey of the literature. *J Nucl Med* 1985; **26**: 258–62.
3. Fish J, Moore RM. Ectopic thyroid tissue and ectopic thyroid carcinoma. *Ann Surg* 1963; **157**: 212.
4. Takahashi T, Ishikura H, Kato H, Tarabe T, Yoshiki T. Ectopic thyroid follicles in the submucosa of the duodenum. *Virchows Arch A Pathol Anat Histopathol* 1991; **418**: 547–50.

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Surgical treatment of reflux stricture of the oesophagus

The choice of surgery in patients with reflux-induced oesophageal stricture remains controversial. From 1976 to 1990, a total of 65 patients underwent fundoplication (36 patients), Collis gastroplasty plus fundoplication (ten), total duodenal diversion (four) and oesophageal resection (15). The postoperative mortality rate was 5 per cent (three patients): necrosis of the colon transplant in two patients and acute pancreatitis in one. The median follow-up was 25 (range 6–120) months. After conservative surgery, the median number of dilatations per patient per year significantly decreased (P < 0·001). Nine patients (25 per cent) complained of persistent or recurrent symptoms after standard fundoplication and six required reoperation. Clinical results were satisfactory in patients who underwent Collis fundoplication, total duodenal diversion and oesophageal resection. It is concluded that the causes of failed fundoplication are irreversible stricture or persistent gastro-oesophageal reflux; the latter may be caused by inefficacy or deterioration of the partial fundoplication wrap. A subtle degree of oesophageal shortening is probably underestimated in such patients and this may explain the better results obtained with the Collis fundoplication. Total duodenal diversion is a good therapeutic option in patients who have undergone previous oesophagogastric surgery. Oesophageal resection should be reserved for patients with tight strictures unresponsive to dilatation or those with scleroderma, multiple previous operations or severe dysplasia in Barrett's oesophagus.

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The surgical treatment of reflux-induced oesophageal stricture remains controversial. The two major areas of debate are the choice of the ideal antireflux procedure and the indication for oesophageal resection.

During the past two decades it has become clear that most strictures can be successfully dilated and that dilatation combined with an antireflux procedure can restore comfortable swallowing in the majority of patients[1,2]. However, in some circumstances oesophageal resection may be the only therapeutic option because of the inability to dilate a long tight stricture or to treat an early recurring stenosis in spite of previous surgical attempts to eliminate gastro-oesophageal reflux[3].

In this retrospective study, management of patients with reflux-induced oesophageal stricture was reviewed to assess the efficacy of various surgical techniques and evaluate the influence of oesophagus-sparing operations on the natural history of the disease.

Patients and methods

From 1976 to 1990, 472 consecutive patients with reflux oesophagitis were referred to the University of Padua Medical School. Of these, 145 (31 per cent) had an oesophageal stricture requiring dilatation. A total of 65 patients were treated surgically during the course of the disease: 39 men and 26 women, of median age 50 (range 15–78) years, with 12 >65 years of age. Ten patients had had previous operations on the upper gastrointestinal tract; these were antireflux procedures (four patients), vagotomy and pyloroplasty (three), partial gastrectomy (two) and Heller's myotomy (one). All 65 patients complained of dysphagia for a median duration of 20 (range 2–180) months and 53 (82 per cent) had a clinical history suggestive of gastro-oesophageal reflux.

Barium contrast studies showed a distal oesophageal stricture; this was associated with a hiatus hernia in the majority of patients. A variable degree of oesophageal shortening was noted in ten patients (15 per cent).

On initial endoscopy, the stenosis did not admit the passage of a paediatric endoscope in 41 patients (63 per cent). In 11 patients (17 per cent) the stricture was not dilatable. The mean(s.d.) length of stricture in 54 patients with a dilatable stenosis was 2·6(0·6) cm. Associated endoscopic findings were erosive oesophagitis in 23 patients (35 per cent), Barrett's oesophagus in 12 (18 per cent) and mid-oesophageal diverticula in two (3 per cent). Severe dysplasia was found in the biopsy specimens of one patient with specialized Barrett's epithelium.

Endoscopic dilatation was always attempted to achieve an adequate oesophageal lumen and patients received medical therapy with H_2-receptor antagonists or, more recently, omeprazole. Dilatation was performed using the Savary–Gilliard bougies (Wilson–Cook, Winston Salem, North Carolina, USA), with positioning of the guidewire under endoscopic control. Vital staining with multiple biopsies and brush cytology of the oesophageal mucosa were routinely performed to exclude malignancy.

Studies of oesophageal function were performed before operation in 42 patients. A motility disorder of the oesophageal body was shown by manometry in 16 individuals (38 per cent): in nine women the manometric pattern was typical of scleroderma and in the remaining seven patients a non-specific motor abnormality was detected. Mean(s.d.) resting pressure of the lower oesophageal sphincter was significantly lower in patients with motility disorders than in 26 healthy control subjects (7·1(3·4) *versus* 23·3(7·2) mmHg, $P < 0·001$). Abnormal oesophageal acid exposure was observed using a standard acid reflux test or 24-h oesophageal pH monitoring in 37 patients (88 per cent).

Table 1 shows the primary surgical procedure performed and associated oesophageal conditions in the 65 patients. Primary surgical treatment was conservative in 50 patients (77 per cent) and consisted of fundoplication in 36, Collis gastroplasty plus fundoplication in ten and total duodenal diversion in four. Intraoperative retrograde dilatation through a gastrotomy was performed in 19 patients.

The fundoplication wrap was partial in 32 patients (30 Toupet, two Dor), total in four (Nissen–Rossetti) and combined with a Collis gastroplasty in ten. The Toupet procedure consisted of posterior hemifundoplication encircling the distal oesophagus for at least 180°. Most of these operations were performed through a laparotomy; a transthoracic approach was used to perform a Collis–Nissen

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fundoplication in two patients. Total duodenal diversion consisted of partial gastrectomy and Roux-en-Y gastrojejunostomy in three patients. In the fourth, who had previously undergone partial gastrectomy, the afferent limb of a Billroth II gastrojejunostomy was sectioned and an end-to-side anastomosis fashioned 50 cm distally. Bilateral truncal vagotomy was added in these patients. Patients who had conservative surgery and needed reoperation or who underwent repeated dilatation beyond the first year of follow-up were considered failures of treatment.

Oesophageal resection was performed as a primary procedure in 15 patients (23 per cent). In five, near-total oesophagectomy was performed without thoracotomy. The continuity of the alimentary tract was re-established using the colon (nine patients), the stomach (four) or the jejunum (two). The anastomosis was intrathoracic in ten patients and cervical in five.

The Mann–Whitney U test was used for statistical analysis.

Results

The postoperative mortality rate was 5 per cent; two patients died from necrosis of the intrathoracic colon transplant and one from acute pancreatitis after a Toupet fundoplication. The morbidity rate was 3 per cent; a minor leakage occurred from one Collis gastroplasty tube and from one intrathoracic oesophagocolic anastomosis. Both patients were successfully treated with prolonged nasogastric decompression, H_2-receptor antagonists and broad-spectrum antibiotics.

The median follow-up was 25 (range 6–120) months. Three patients died from unrelated disease 8, 11 and 37 months after operation. One patient died from squamous cell oesophageal cancer 78 months after successful fundoplication; 4 months earlier this patient had been treated by prosthetic intubation because of local tumour spread and high operative risk.

The need for subsequent dilatations was markedly reduced in patients undergoing conservative surgery. The median (range) number of dilatations per patient per year decreased from 3 (1–8) to 0 (0–4) ($P < 0{\cdot}001$). Only eight patients underwent further dilatation after the first year of follow-up.

Table 1 *Details of primary surgical procedures and associated oesophageal conditions in 65 patients*

	No.	Previous surgery	Scleroderma	Barrett's oesophagus
Fundoplication				
Toupet	28	2	5	4
Nissen–Rossetti	6	1	0	2
Dor	2	0	0	0
Gastroplasty plus fundoplication				
Collis–Nissen	8	0	1	2
Collis–Toupet	2	1	2	0
Total duodenal diversion	4	4	0	1
Oesophageal resection	15	2	1	3

The results of fundoplication were satisfactory in 27 of the 36 patients (75 per cent). Nine patients presented with persistent or recurrent symptoms (*Table 2*); three, including one with scleroderma, had gastro-oesophageal reflux demonstrated on pH studies after a Toupet fundoplication and were treated with medical therapy and repeated dilatation. Six of these nine required reoperation for intractable symptoms. Four patients with persistent dysphagia secondary to an irreversible stricture and one with scleroderma underwent oesophageal resection and reconstruction using colon (two patients), stomach (two) or jejunum (one). Near-total oesophagectomy with cervical oesophagogastrostomy was performed without thoracotomy in two patients. One patient with severe reflux symptoms after partial fundoplication underwent total duodenal diversion. Of interest is that five of the six patients who required further surgery had a long (>2 cm) and tight (<10 mm) stricture on initial endoscopy (*Table 2*).

The clinical results of the Collis fundoplication procedures were satisfactory in all ten patients. Of the four who underwent total duodenal diversion, one complained of mild dyspepsia caused by delayed gastric emptying. Regression of Barrett's epithelium was not observed after any conservative surgical procedure.

There were no deaths following reoperation after conservative surgery. A minor leak from the intrathoracic oesophagogastric anastomosis in one patient healed with medical therapy.

The clinical results of oesophageal reconstruction were satisfactory in the 18 patients (13 primary, five secondary procedures) who survived the operation. Of these patients, five required one to four postoperative dilatations for a cervical (three) or intrathoracic (two) anastomotic stricture; all patients received dilatation within the first year of follow-up. Pathological examination of the resected specimen confirmed the preoperative diagnosis of specialized columnar-lined epithelium with severe dysplasia in one of the patients who died from necrosis of the colon transplant.

Discussion

Current surgical options for treatment of reflux stricture of the oesophagus include a variety of oesophagus-sparing operations: partial and total fundoplication, Collis gastroplasty plus fundoplication and total duodenal diversion. Oesophageal resection is usually reserved for patients with undilatable strictures or after the failure of conservative techniques.

The generally applied criteria for selecting the most appropriate surgical procedure are oesophageal length, as determined by conventional barium swallow study, stricture length, as measured endoscopically, and the degree of fibrosis,

Table 2 *Clinical data of nine patients in whom primary fundoplication was unsuccessful*

Patient no.	Stricture Length (cm)	 Diameter (mm)	Associated disease	Type of fundoplication	Lower oesophageal sphincter pressure after operation (mmHg)	Gastro-oesophageal reflux	Reoperation
1	1	4	—	Toupet	6·5	Yes	—
2	2	11	—	Toupet	9	Yes	—
3	1	10	Scleroderma	Toupet	n.a.	Yes	—
4	1	11	Scleroderma	Toupet	6	Yes	Oesophagogastroplasty
5	2	8	Barrett's oesophagus	Toupet	8·3	Yes	Total duodenal diversion
6	2	6	Barrett's oesophagus	Toupet	11	No	Oesophagojejunoplasty
7	4	1	—	Toupet	n.a.	No	Oesophagocoloplasty
8	5	1	—	Toupet	13	No	Oesophagocoloplasty
9	3	8	Kyphoscoliosis	Nissen	18	No	Oesophagogastroplasty

n.a., Not available

as felt on preoperative dilatation. Unfortunately, no other investigations are available to date to measure the degree of transmural fibrosis, although endoscopic ultrasonography may prove to be of value. This makes it difficult to predict the need for oesophageal resection and may in part account for the reported treatment failures with conventional antireflux operations[4].

Despite the lack of controlled trials comparing dilatation and surgical treatment in long-term follow-up, the addition of an antireflux repair after proper dilatation seems more reasonable than lifelong endoscopic dilatation and medication in selected patients with reflux-induced oesophageal stricture. The present study shows that antireflux surgery favourably affects the natural history of the disease by reducing the need for subsequent dilatation. However, a full-thickness stricture can restenose even if a successful antireflux procedure accompanies dilatation, and this was indeed the cause of a failed fundoplication in four patients of the present series. These patients required oesophageal resection to obtain symptomatic relief.

On the other hand, partial fundoplication, such as the Toupet procedure, may be inadequate to prevent reflux. Deterioration of the valve over time has been demonstrated in a prospective study of this technique using 24-h oesophageal pH monitoring[5].

It is suspected that unrecognized longitudinal tension on the antireflux repair could have adversely affected the outcome of the partial fundoplication in two patients in the present series who required reoperation and in three who were treated medically. The results with the Collis fundoplication have been satisfactory, even in patients with scleroderma, supporting the hypothesis that oesophageal shortening can contribute to the failure of standard antireflux procedures by precluding adequate mobilization of the cardia[6–8]. Although a good mediastinal dissection at laparotomy is mandatory to achieve a sufficient length of intra-abdominal oesophagus[1], this manoeuvre alone may not be successful in the presence of perioesophagitis or true oesophageal shortening. The Collis gastroplasty can be performed easily through the abdominal approach using a circular stapler to suture both gastric walls at the distal limit of the proposed gastric tube and then applying the GIA stapler (US Surgical, Norwalk, Connecticut, USA) parallel to the lesser curve with a calibrating bougie inside the visceral lumen[9].

Total duodenal diversion has proven effective in the present series, although the number of patients is too small to warrant further comment. This indirect approach to the treatment of oesophageal stricture provides effective acid suppression and diversion of duodenal contents[10–14]; it is particularly indicated when neither the distal oesophagus nor the proximal stomach is approachable because of a dense inflammatory reaction to previous surgery or when no fundus is available for plication owing to previous gastric resection. If the vagus nerves cannot be reached and identified at laparotomy, vagotomy may be performed by opening the diaphragm anterior to the oesophageal hiatus or through a left thoracotomy. Thoracoscopic vagotomy is a promising alternative[15]. When the gastric remnant has one-third or less of the original capacity of the stomach, vagotomy may be avoided, but this choice will probably require lifelong pharmacological therapy to prevent the occurrence of a marginal ulcer[12].

Improvements in the technique of endoscopic dilatation have relegated the use of resection to a restricted subgroup of patients. Resection remains necessary when adenocarcinoma arising from Barrett's oesophagus is strongly suspected[16,17] or when the frequency of dilatation interferes with the patient's lifestyle; this usually occurs in individuals with multiple previous operations or a severe oesophageal motility disorder[18–20]. The decision to perform resection at the first operation is difficult because there are no absolute objective criteria to establish whether the patient could benefit from an initial conservative approach. Although the long-term results of colon interposition are excellent[21], the incidence of necrosis is about 10 per cent[22]. It is agreed with others[3,18,19] that the stomach can be safely used as an oesophageal substitute, provided that anastomosis is performed at the apex of the chest or in the neck.

It can be concluded that antireflux surgery may favourably influence the natural history of oesophageal stricture. To achieve this, surgical treatment should be undertaken early in the course of the disease to avoid progressive transmural fibrosis and further functional damage secondary to repetitive dilatation. Subtle oesophageal shortening, undetected before or during operation, may be more frequent than generally appreciated and may explain the high failure rate in patients undergoing standard fundoplication.

Most patients with a short and easily dilatable stricture can be successfully treated with a Toupet or Nissen–Rossetti fundoplication in an early stage of disease. A partial wrap is preferable in those with scleroderma to prevent oesophageal obstruction. The Collis fundoplication and total duodenal diversion are better surgical options in patients with suspected oesophageal shortening or previous oesophagogastric surgery respectively. Resection should be reserved only for patients with long and undilatable strictures, advanced scleroderma, multiple previous operations, and severe dysplasia or adenocarcinoma in Barrett's oesophagus. Transhiatal oesophagectomy represents an excellent surgical approach in such patients.

References

1. Watson A. Reflux stricture of the oesophagus. *Br J Surg* 1987; **74**: 443–8.
2. Bonavina L, Norberto L, Cusumano A *et al.* Reflux-induced esophageal strictures: factors influencing long-term results of dilatation. In: Little A, Ferguson M, Skinner D, eds. *Diseases of the Esophagus*. Vol. II. New York: Futura Publishing, 1990: 247–54.
3. Little AG, Naunheim KS, Ferguson MK, Skinner DB. Surgical management of esophageal strictures. *Ann Thorac Surg* 1988; **45**: 144–7.
4. Siewert R. Surgical therapy of peptic stenoses. In: Stipa S, Belsey R, Moraldi A, eds. *Medical and Surgical Problems of the Esophagus*. London: Academic Press, 1981: 146–54.
5. Galmiche J, Teniere P, Ducrotte P, Denis P, Colin R, Testart J. Traitement du reflux gastro-oesophagien acide par hemifundoplicature postérieure. Résultats cliniques et pHmétriques. *Gastroenterol Clin Biol* 1983; **7**: 385–91.
6. Pearson FG, Cooper JD, Patterson GA, Ramirez J, Todd TR. Gastroplasty and fundoplication for complex reflux problems. *Ann Surg* 1987; **206**: 473–81.
7. Stirling MC, Orringer MB. The combined Collis–Nissen operation for esophageal reflux strictures. *Ann Thorac Surg* 1988; **45**: 148–57.
8. Duranceau A. Evolving techniques in the management of benign esophageal stricture. *Ann Thorac Surg* 1989; **48**: 322–3.
9. Steichen F. Abdominal approach to the Collis gastroplasty and Nissen fundoplication. *Surg Gynecol Obstet* 1986; **162**: 272–4.
10. Payne W. Surgical management of reflux-induced oesophageal stenoses. Results in 101 patients. *Br J Surg* 1984; **71**: 971–3.
11. Washer G, Gear M, Dowling B, Gillison E, Royston C, Spencer J. Duodenal diversion with vagotomy and antrectomy for severe or recurrent reflux oesophagitis and stricture: an alternative to operation at the hiatus. *Ann R Coll Surg Engl* 1986; **68**: 222–6.
12. Perniceni T, Mosnier H, Gayet B, Fékété F. Traitement des oesophagites peptiques compliquées. Place de la diversion duodenale totale. *Presse Med* 1989; **18**: 819–22.
13. Ellis FH, Gibb SO. Esophageal reconstruction for complex benign esophageal disease. *J Thorac Cardiovasc Surg* 1990; **99**: 192–9.
14. Salo JA, Ala-Kullju KV, Heikkinene LO, Kivilaakso EO. Treatment of severe peptic esophageal stricture with Roux-en-Y partial gastrectomy, vagotomy, and endoscopic dilation. *J Thorac Cardiovasc Surg* 1991; **101**: 649–53.
15. Chisholm E, Chung S, Sunderland G, Leong H, Li A. Thoracoscopic vagotomy: a new use for the laparoscope. *Br J Surg* 1992; **79**: 254.
16. Skinner D, Walther B, Riddell R, Schmidt H, Iascone C,

DeMeester TR. Barrett's esophagus: comparison of benign and malignant cases. *Ann Surg* 1983; **198**: 554–65.
17. DeMeester T, Attwood S, Smirk T, Therkildsen D, Hinder R. Surgical therapy in Barrett's esophagus. *Ann Surg* 1990; **212**: 528–42.
18. Waters PF, Pearson FG, Todd TR *et al.* Esophagectomy for complex benign esophageal disease. *J Thorac Cardiovasc Surg* 1988; **95**: 378–81.
19. Orringer MB, Stirling M. Cervical esophagogastric anastomosis for benign disease: functional results. *J Thorac Cardiovasc Surg* 1988; **96**: 887–93.
20. Mansour K, Malone C. Surgery for scleroderma of the esophagus: a 12-year experience. *Ann Thorac Surg* 1988; **46**: 513–14.
21. Skinner D, Belsey R. *Management of Esophageal Disease.* Philadelphia, Pennsylvania: WB Saunders, 1988.
22. Postlethwait R. Colonic interposition for esophageal substitution. *Surg Gynecol Obstet* 1983; **156**: 377–83.

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Surgical workshop

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Thoracoscopy in oesophagectomy for oesophageal cancer

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Treatment of oesophageal cancer in this department usually involves a three-stage procedure including a right thoracotomy to determine the degree of oesophageal resection and the stage of the tumour. This is followed by laparotomy to create a gastric tube and a left-sided cervical incision to allow the resection and creation of the cervical anastomosis. Since May 1991, eight oesophagectomies for cancer have been performed using thoracoscopy instead of a thoracotomy; this article describes the technique and preliminary results.

Surgical technique

From May 1991 to March 1992, eight patients (six men and two women; mean age 60 (range 43–72) years) underwent oesophagectomy for cancer in which thoracotomy was replaced by thoracoscopy. The site of the tumour was the upper third of the oesophagus in one patient, the middle third in five and the lower third in two. None of the patients received preoperative chemotherapy or radiotherapy. All underwent surgical thoracoscopy as the first step.

General anaesthesia was performed with a double-lumen endotracheal tube. Patients were placed in a left lateral decubitus position with a tilt to the right. The arm was kept in abduction to ensure maximal superior displacement of the scapula. Five cannulas were placed as shown in *Figure 1*. The first cannula was inserted in the fifth intercostal space below the lower pole of the scapula. Carbon dioxide insufflation to a maximum pressure of 6 mmHg was used.

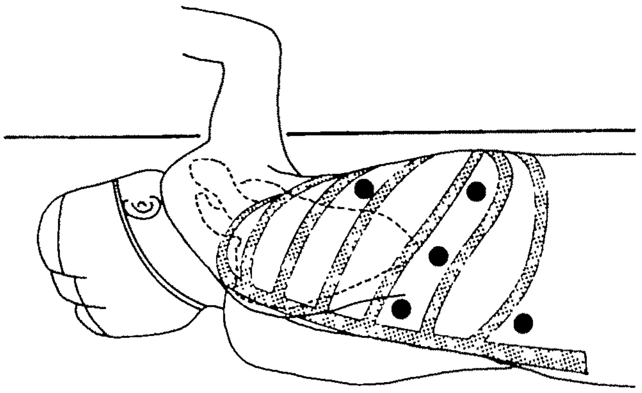

Figure 1 *Site of insertion of thoracoscopic cannulas. Two posterior cannulas (12 mm in diameter) are used for introduction of the grasping forceps and/or loops. Two anterior cannulas (12 mm in diameter) allow the insertion of grasping forceps, coagulating scissors, clip applicators and the Endo-GIA. The cannula sited below the pole of the scapula is used for the introduction of the 10-mm telescope and the Endo-Clip (US Surgical) or Endo-GIA*

The combined effect of insufflation, selective aspiration of air from the right lung by the endotracheal tube and gentle mechanical compression of the lung by the laparoscope resulted in complete collapse of the right lung.

The first step in the procedure is the evaluation of the local extent of the tumour. The mediastinal and parietal pleura is dissected using coagulation scissors to enable a loop to be passed around the oesophagus.

The oesophagus is then pulled up to expose its vessels, which are clipped or coagulated. Division of the azygos vein is performed by application of an Endo-GIA (US Surgical, Norwalk, Connecticut, USA) stapler. Paraoesophageal and paratracheal lymph nodes are completely dissected and removed. After complete mobilization of the oesophagus, a short transverse laparotomy incision is created to allow formation of a gastric tube by excision of the lesser curvature, and full gastric mobilization. The cervical oesophagus is mobilized through a neck incision and the gastric tube brought up for manual creation of a cervical anastomosis. The thoracic oesophagus was completely mobilized thoracoscopically in seven patients. The eighth patient required transhiatal digital mobilization.

Results

The mean time required to perform thoracoscopy was 180 min. The mean operative blood loss during endoscopic dissection was 600 (range 400–800) ml. There were no deaths.

The only peroperative difficulties were a request from the anaesthetic team for intermittent pulmonary re-expansion and one case of haemorrhage from an intercostal artery caused by passage of a cannula.

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One patient developed a pulmonary infection and, approximately 2 days after surgery, six others showed radiological evidence of oedematous lesions on the right side resulting from poor pulmonary re-expansion. One patient developed an anastomotic fistula confirmed by water-soluble contrast swallow.

Discussion

Thoracoscopy applied as the first step in the treatment of oesophageal cancer is a useful technique to evaluate the local extent of disease and therefore the resectability, so as to avoid a fruitless exploratory thoracotomy with its complications[1–3]. Thoracoscopy enables individual planning of surgery with the minimum of surgical trauma[4]. Also, the oesophagus is easily freed under thoracoscopic visualization[5,6]. This seems to be more effective than any other resection with a closed thorax, and reduces the potential for complications[7,8]. Finally, this approach allows an identical oncological clearance to other methods. Further experience is necessary to allow statistically significant comparison. Further development of percutaneous instrumentation and increasing experience should reduce the time required for thoracoscopy, and should improve the accuracy of staging and the completeness of resection.

References

1. King RM, Pairolero PC, Trastek VF, Payne WS, Bernats PE. Ivor–Lewis esophagogastrectomy for carcinoma of the esophagus: early and late functional results. *Ann Thorac Surg* 1987; **44**: 119–22.
2. Postlethwait RW. Complications and deaths after operations for oesophageal carcinoma. *J Thorac Cardiovasc Surg* 1983; **85**: 827–31.
3. Skinner DB. *En bloc* resection for neoplasm of oesophagus and cardia. *J Thorac Cardiovasc Surg* 1983; **85**: 59–71.
4. Behamou G, Marmuse JP, Johanet H, Le Goff JY, Hecht F. Notre schéma thérapeutique dans les cancers avancés de l'oesophage. *J Chir* (*Paris*) 1990; **127**: 518–21.
5. Cuschieri A, Shimi S, Banting S. Endoscopic oesophagectomy through a right thoracoscopic approach. *J R Coll Surg Edinb* 1992; **97**: 7–11.
6. Gossot D, Ghnassia MD, Debiolles H *et al.* Thoracoscopic dissection of the esophagus: an experimental study. *Surg Endosc* 1992; **6**: 59–61.
7. Hankins JR, Miller JE, Attar S, McLaughlin JS. Transhiatal esophagectomy for carcinoma of the esophagus: experience with 26 patients. *Ann Thorac Surg* 1987; **44**: 123–7.
8. Orringer MB. Transhiatal esophagectomy without thoracotomy for carcinoma of thoracic esophagus. *Ann Surg* 1984; **200**: 282–8.

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Monofilament *versus* multifilament absorbable sutures for abdominal closure

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*This study compares monofilament continuous absorbable sutures with multifilament interrupted absorbable sutures for abdominal closure. Before closure of an abdominal incision, 988 patients were randomized to receive either a monofilament polyglyconate (Maxon) or a multifilament polyglactin 910 (Vicryl) suture. At 1 year after operation, 684 patients (69 per cent) were examined for the presence of incisional hernia, sinus and other wound-healing problems; 179 (18 per cent) had died and 125 (13 per cent) did not attend for follow-up. Incisional hernia occurred in 8 per cent of patients receiving monofilament continuous sutures compared with 6 per cent of those having multifilament interrupted closure (*P *not significant). Wound dehiscence occurred in 1 per cent of both groups. The mean time for suturing was 7·1 min for monofilament continuous and 8·7 min for multifilament interrupted sutures (*$P < 0.001$*). It is concluded that closure of an abdominal incision can be effected by a monofilament continuous absorbable suture more quickly than by multifilament interrupted absorbable sutures without an increased risk of wound dehiscence or incisional hernia.*

Secure wound closure is essential for an uncomplicated and appropriate recovery after abdominal surgery. The most serious wound complications are dehiscence, incisional hernia and infection. These complications are closely related to the condition of the patient, type of incision, suturing technique and material used for suturing. The best method of wound closure is one that provides adequate tensile strength to the tissue until the wound is healed, permits normal healing and remains secure even in the presence of infection[1]. Non-absorbable multifilament sutures have a higher incidence of wound infection and sinus formation[1–3]. A continuous suture has the advantage of even distribution of tension across the suture line and is a faster method of closure; a disadvantage is that closure relies on a single suture line. The multiple interrupted suture is safe and has been in use for many years, but has the disadvantages of being time consuming and producing an uneven tension in the wound tissues[4]. Thus, it is still disputed which technique and which suture material are preferable for wound closure[5,6].

The purpose of the present study was to compare a monofilament continuous absorbable suture with a multifilament interrupted absorbable suture by recording the incidence of wound dehiscence and incisional hernia, and the time required for suturing.

Patients and methods

Patients

The study group comprised 988 consecutive patients who underwent abdominal surgery; emergency cases were included. Experience varied greatly among the 25 surgeons who performed the operations. Patients with muscle-splitting incisions were excluded. Immediately before closure of the abdominal incision patients were randomized using sealed numbered envelopes to receive either a monofilament continuous absorbable or a multifilament interrupted absorbable suture. Randomization was not stratified.

The age, sex, weight, height, haemoglobin level, presence of malignancy at surgery, previous radiotherapy, use of steroids and signs of infection at surgery were noted, as was the time required to close the abdominal wall, including the tying of knots, measured with a stopwatch. Patients were divided into five different groups with regard to the type of surgery and into four groups regarding the type of incision. They were asked to attend 1 year after surgery for follow-up examination. At this visit any reoperations, the presence of incisional hernia and postoperative dehiscence, infection, suture granuloma and other wound-healing problems were recorded. The abdominal scar was measured; the scar length was considered to be the same as the wound length. Incisional hernia was recorded as a protrusion in the wound, revealed on careful examination when the patient lifted the legs upward while lying in the supine position. The record sheet used at the follow-up examination did not reveal the suturing technique to the examiner.

The protocol was approved by the ethical committee at Karolinska Institute.

Materials

For monofilament continuous closure the absorbable suture material used was polyglyconate (Maxon size 0; Davis and Geck, Gosport, UK). At the beginning of the continuous suture a half blood-knot was made and the suture ended with an Aberdeen knot[7,8]. Surgeons were instructed to perform the suture with large bites and close stitches.

In the multifilament interrupted group the material was polyglactin 910 (Vicryl size 0; Ethicon, Norderstedt, Germany) with interrupted far-and-near sutures and ordinary surgical knots; this was previously the standard suturing technique in the department.

Statistical analysis

Significance of differences was evaluated by the Mann–Whitney U test, Fisher's exact test and χ^2 analysis. Data are presented as mean(s.d.). $P < 0.05$ was considered significant.

To calculate the power of the study, it was assumed that a difference in the incidence of hernia of 5 per cent in one group and 10 per cent in the other would be clinically relevant. For a significance level of $\alpha = 0.05$ and $\beta = 0.1$, approximately 400 patients per group would be required. With this number of patients a difference in the frequency of burst abdomen of 1–4 per cent could also be confirmed as significant. Approximately 500 patients were entered in each group.

Results

Of the 988 patients in the study, 684 (69 per cent) were available for follow-up 1 year after surgery; 179 patients (18 per cent) had died and 125 (13 per cent) did not attend for follow-up. None of the patients who died was reported to have had a hernia or dehiscence. The clinical features of the two groups were similar (*Table 1*).

Hernia occurred in 28 patients (8 per cent) receiving monofilament continuous sutures compared with 21 (6 per cent)

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of those with multifilament interrupted closure (*P* not significant). Wound dehiscence occurred in four patients (1 per cent) and in three (1 per cent) respectively. The incidence of wound infection was 10 per cent (35 patients) in the monofilament continuous and 11 per cent (37) in the multifilament interrupted group. No sinus formation was reported (*Table 2*).

The mean(s.d.) time for suturing was 7·1(3·6) min in patients receiving monofilament continuous sutures and 8·7(4·3) min in those with multifilament interrupted closure ($P < 0{\cdot}001$). Mean(s.d.) suturing time related to the incision length was 0·49(0·24) and 0·57(0·25) min/cm respectively ($P < 0{\cdot}001$) (*Table 2*).

The distribution of complications with different types of incision is shown in *Table 3*. There were 13 cases (4 per cent) of hernia but none of dehiscence in patients with a subcostal incision. Complications were most common in midline incisions, with 31 cases (10 per cent) of hernia and five of dehiscence (2 per cent). After paramedian incision there were five hernias (7 per cent) and two dehiscences (3 per cent). There was no significant difference between the midline incision and all the other types of incision.

Table 1 *Details of 684 patients undergoing abdominal surgery*

	Monofilament continuous closure	Multifilament interrupted closure
No. of patients	345	339
Age (years)*	58(17)	58(17)
Sex ratio (M:F)	118:227	135:204
Height (cm)*	169(8)	170(10)
Weight (kg)*	70(20)	73(21)
Plasma haemoglobin level (g/l)*	135(18)	138(16)
Emergency procedure	94	89
Malignancy	65	60
Infection present at surgery	33	21
Preoperative diabetes, use of steroids, abdominal radiation	14	12
Type of surgery		
Upper gastrointestinal tract	54	59
Hepatopancreatobiliary	143	141
Lower gastrointestinal tract	123	122
Vascular	11	11
Other	14	6

*Values are mean(s.d.). There were no significant differences between groups

Table 2 *Follow-up of 684 patients 1 year after abdominal surgery*

	Monofilament continuous closure ($n = 345$)	Multifilament interrupted closure ($n = 339$)	*P*
Dehiscence	4	3	n.s.†
Incisional hernia	28	21	n.s.†
Wound infection	35	37	n.s.†
Incision (cm)*	15·2(4·8)	15·4(4·9)	n.s.‡
Suturing time (min)*	7·1(3·6)	8·7(4·3)	<0·001‡
Suture rate (min/cm)*	0·49(0·24)	0·57(0·25)	<0·001‡

*Values are mean(s.d.). †Fisher's exact test; ‡Mann–Whitney *U* test; n.s., not significant

Discussion

Closure of different types of abdominal incision may be performed in a multitude of ways[9,10]. New materials and sutures are regularly introduced. In Sweden, two of the most common abdominal closure techniques use multifilament interrupted absorbable and monofilament continuous absorbable sutures. These two techniques were compared in the present study. Continuous suture with a multifilament absorbable thread was not chosen because this combination results in a higher incidence of incisional hernia[5]; non-absorbable sutures were not used, to avoid the potential problems of late sinus and suture-related wound pain.

This prospective randomized study of patients, which included those undergoing both elective and urgent operations, has shown no significant differences in rates of wound dehiscence or hernia between the continuous and interrupted methods of wound closure. The numbers followed at 1 year in each group did not reach the target set by the power calculation. However, it was not considered necessary to recruit more patients because the hernia rate was lower than the 10 per cent assumed in the power calculation and the difference between the groups was much less than the 50 per cent reduction assumed. A very much larger study would be required to determine whether a difference between 6 and 8 per cent is statistically significant, and such a difference is unlikely to be clinically important. The reason for the lower than expected number of patients at follow-up was a combination of failure to attend and a high 1-year mortality rate (18 per cent). Emergency operations accounted for 27 per cent of the procedures included in the study. This may explain the high mortality rate observed at 1 year.

The dehiscence rate of 1 per cent for both methods is similar to those of other reports[1,2,4,9–11]. The incidence of incisional hernia at 1-year follow-up was similar in the two groups, at 8 and 6 per cent. The incidence of hernia in most reviews[2] is between 5 and 10 per cent, but follow-up is often shorter than in this study.

The midline incision resulted in a 12 per cent incidence of hernia and dehiscence compared with 4 per cent for subcostal or transverse incisions and 10 per cent for the paramedian incision, but there were no differences with each type of incision related to wound closure technique.

Some hernias in the patients receiving monofilament continuous closure at the start of the study could have resulted from the use of an unfamiliar suturing and knotting technique. Use of a suture three times the length of the incision was recommended to ensure that tissue bites were deep enough.

Table 3 *Type of incision in 684 patients undergoing abdominal surgery*

	Monofilament continuous closure			Multifilament interrupted closure		
Type of incision	No.	Hernia	Dehiscence	No.	Hernia	Dehiscence
Midline	148	20	4	155	11	1
Paramedian	39	1	0	32	4	2
Subcostal or transverse	155	7	0	148	6	0
Other	3	0	0	4	0	0
Total	345	28	4	339	21	3

There were no significant differences between groups (χ^2 test)

However, Jenkins[12] has shown that a length of at least four times the wound length is desirable. A longer suture:wound length ratio might have reduced the incisional hernia rate in this group.

The two methods were found to be equal regarding wound-healing problems, but monofilament continuous suturing was faster. The suture used in the monofilament continuous group is now available in loop form, making the first knot unnecessary, which may further shorten the suturing time.

In conclusion, closure of an abdominal incision with a monofilament continuous absorbable suture was faster than that with a multifilament interrupted absorbable suture, with no increase in the rate of wound dehiscence or hernia.

References

1. Wadström J, Gerdin B. Closure of the abdominal wall: how and why? *Acta Chirurgica Scandinavica* 1990; **156**: 75–82.
2. Leaper DJ. Laparotomy closure. *Br J Hosp Med* 1985; **6**: 317–22.
3. Poole GV Jr. Mechanical factors in abdominal wound closure: the prevention of fascial dehiscence. *Surgery* 1985; **97**: 631–9.
4. Richards PC, Balch CM, Aldrete JS. Abdominal wound closure. A randomized prospective study of 571 patients comparing continuous *vs* interrupted suture techniques. *Ann Surg* 1983; **197**: 238–43.
5. Wissing J, van Vroonhoven ThJMV, Schattenkerk ME, Veen HF, Ponsen RJK, Jeekel J. Fascia closure after midline laparotomy: results of a randomized trial. *Br J Surg* 1987; **74**: 738–41.
6. Fagniez P-I, Hay JM, Lacàine F, Thomsen C. Abdominal midline incision closure. *Arch Surg* 1985; **120**: 1351–3.
7. Wattchow DA, Watts JMcK. The half blood knot for tying nylon in surgery. *Br J Surg* 1984; **71**: 333.
8. Paterson-Brown S, Dudley HAF. Knotting in continuous mass closure of the abdomen. *Br J Surg* 1986; **73**: 679–80.
9. Ellis H, Bucknall TE, Cox PJ. Abdominal incisions and their closure. *Curr Probl Surg* 1985; **22**: 5–50.
10. Krukowski ZH, Cusick EL, Engeset J, Matheson NA. Polydioxanone or polypropylene for closure of midline abdominal incisions: a prospective comparative clinical trial. *Br J Surg* 1987; **74**: 828–30.
11. McNeill PM, Sugerman HJ. Continuous absorbable *vs* interrupted nonabsorbable fascial suture. *Arch Surg* 1986; **121**: 821–3.
12. Jenkins TPN. The burst abdominal wound: a mechanical approach. *Br J Surg* 1976; **63**: 873–6.

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Early gastric cancer: follow-up after gastrectomy in 159 patients

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The postoperative course of 159 patients with early gastric cancer operated on between 1974 and 1987 was followed for a median of 7·3 years. The cumulative 10-year survival rate(s.e.) calculated using follow-up data to the end of 1989 was 90·6(2·7) per cent excluding operative death and that from causes other than gastric cancer, or 86·3(3·0) per cent when operative mortality was included. The overall 10-year survival rate(s.e.) was 77·3(3·7) per cent. Univariate analysis showed a significant difference in survival rates between cancers confined to the mucosa and those with submucosal invasion ($P = 0{\cdot}02$)*, between patients with and without lymph node metastases* ($P = 0{\cdot}05$) *and between those* ≤ 50 *and* >50 *years of age* ($P = 0{\cdot}02$)*. Using Cox multivariate analysis and a stepwise procedure for eight variables (sex, age, depth of invasion, lymph node metastases, presence of ulceration, location, histological type, type of surgery), age and histological type had the most significant effect on survival. Seven operative deaths were recorded. Eleven patients died from recurrent cancer and one is still alive with a gastric remnant recurrence. Other causes of death were metachronous primary cancer (six patients), cardiovascular disease (two), pneumonia (three), sepsis (one) and car accident (one). Although the prognosis of early gastric cancer is relatively good in western countries, patients should be carefully followed over a long period for late recurrence and for metachronous cancer, which has a high incidence.*

In Japan the proportion of early gastric cancers (EGCs) treated has risen[1] from 9·4 per cent for the period 1963–1966 to 43·8 per cent during 1979–1987. In the USA[2] the overall proportion of gastric cancers diagnosed early is only 3·7 per cent and European series[3] report a value <10 per cent. In Italy[4] there has been a clear increase in the diagnosis of EGC, from 6 per cent in 1980 to about 12 per cent in 1985.

Curative endoscopic treatment of EGC, either by endoscopic excision or laser therapy, has been reported[5–8], but is reserved strictly for selected indications (about 10 per cent of EGCs) and is possible only after preoperative assessment of the depth of tumour invasion and lymph node involvement by endosonography[9].

Two main types of operative procedure are employed for the treatment of EGC: subtotal (or distal) and total gastrectomy. Controversy still exists regarding the choice of the most suitable procedure. The number of proximal gastrectomies performed for EGC of the upper third of the stomach is decreasing because of the poor outcome if anastomotic leakage develops[10] and because of a high rate of local recurrence resulting in a significantly lower 5-year survival rate in comparison with total gastrectomy[11,12].

The results of long-term follow-up studies for EGC are just beginning to appear. This paper reports a 10-year follow-up study of 159 surgically treated patients with EGC.

Patients and methods

Between 11 June 1974 and 30 November 1987, 171 patients with EGC underwent operation in six central Italian surgical departments by the senior author or surgeons trained by him. This represents 14·4 per cent of the 1186 gastric cancers of all types treated in the six units over the same period. The diagnosis of EGC was made according to the criteria of the general rules for gastric carcinoma from the Japanese Research Society for Gastric Cancer (JRSGC)[13,14]. Twelve patients with two or more tumours in the stomach were excluded, leaving 159 cases of single EGC for analysis.

A total of 68 cases of EGC were diagnosed in the first 7 years, the other 91 in the last 7. The difference between the two periods is probably related only to better diagnosis and does not represent an increase in incidence. Diagnosis was made by radiology in six patients (3·8 per cent), at endoscopy in 58 (36·5 per cent) and after operation in the remaining 95 (59·7 per cent). Based on preoperative endoscopic biopsy, 91 of these 95 patients were diagnosed as having stomach cancer; in four with negative biopsy the preoperative diagnosis was gastric ulcer.

All 28 patients with cancer of the upper third of the stomach underwent total gastrectomy with lymphadenectomy involving gastric and perigastric nodes (groups 1 and 2 nodes according to the JRSGC; R_2 resection). Forty patients with tumours in the inferior two-thirds of the stomach underwent total gastrectomy–R_2, the remaining 91 subtotal gastrectomy with incomplete dissection of the gastric and perigastric nodes ($R_{0/1}$). Resected specimens were prepared, fixed and sectioned according to the rules of the Japanese Research Society Committee on histological classification of gastric cancer[14].

Follow-up

Patients were seen 6 months after operation and yearly thereafter. Each patient underwent both clinical and laboratory assessment, including endoscopy with biopsy. Many patients were evaluated by upper gastrointestinal radiography, ultrasonography, radionuclide scan, computed tomography, magnetic resonance imaging and nutritional interview. Demographic information available on 31 December 1989 was used. No patient was lost to follow-up. The follow-up ranged from 2 to 15 (median 7·3) years.

Patient charts, operation notes and histopathology reports of the resected specimens were reviewed. The 159 tumours were macroscopically subdivided into ulcerated (IIc, III, IIa + IIc, IIc + IIa, IIc + III, III + IIc) and non-ulcerated (I, IIa, IIb, IIa + IIb) types; mixed lesions were classified according to the predominant macroscopic pattern. Microscopic division into intestinal and non-intestinal types, the latter including diffuse, mixed and unclassified EGC, was according to Laurén[15]. Depth of invasion was also studied microscopically, distinguishing the forms affecting only the mucosal layer from those also involving the submucosa.

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Statistical analysis

Estimates of the cumulative 10-year survival probabilities were calculated according to the Kaplan–Meier[16] method for the entire series (159 patients), and after excluding operative mortality (152), mortality from other causes (146), and both operative and other causes of mortality (139). The endpoint in the analysis was death from any cause.

Univariate analysis (Kaplan–Meier method) was used to calculate the cumulative 5- and 10-year survival probabilities in relation to the following eight clinical and histopathological variables: age ($\leqslant 50$, 51–57, $\geqslant 58$ years), sex, tumour location (upper, middle and lower thirds), macroscopic type (ulcerated, non-ulcerated), depth of invasion (mucosal, submucosal), histological type (intestinal, non-intestinal), presence or absence of lymph node metastasis, and type of surgery (total gastrectomy–R_2 or subtotal gastrectomy–$R_{0/1}$). The difference between curves was assessed using the log rank test[17]; estimated relative hazards and their 95 per cent confidence intervals were calculated by treating each life-table interval as a separate stratum and comparing the two life-tables within each stratum according to the Mantel–Haenszel procedure[18].

Because these variables are simultaneously related to the prognosis of EGC, multivariate analysis was performed using the Cox proportional hazards model[19]. The relative risk for each significant variable was then calculated by considering favourable or unfavourable values of that variable, assuming that other variables were at their mean value. Risk ratios were then obtained for each single significant variable of the Cox proportional hazards model. The risk ratio indicates how many times the death risk of the unfavourable variable is higher than that of the favourable one.

Finally, hazard ratios were calculated. These are prognostic indices indicating the risk of death for a patient with a given set of values of the significant variables compared with that of a patient who has a mean value for every variable.

Results

The ages of the patients with EGC ranged from 24 to 76 (mean 55·3) years. The male:female ratio was 1·27:1. In all, 28 of the lesions (17·6 per cent) were located in the upper third of the stomach, 62 (39·0 per cent) in the body and 69 (43·4 per cent) in the antrum (*Table 1*). Histological analysis showed non-ulcerated type in 47 lesions (29·6 per cent) and ulcerated in 112 (70·4 per cent). Depth of invasion was restricted to the mucosa in 55 patients (34·6 per cent) and in 104 (65·4 per cent) was as far as the submucosa but not beyond. Microscopically, 73 tumours (45·9 per cent) were of non-intestinal and 86 (54·1 per cent) of intestinal type. No age difference was detected between patients with EGC of intestinal and non-intestinal types ($\chi^2 = 0{\cdot}14$; 2 d.f., $P = 0{\cdot}9$). The presence of lymph node metastasis was demonstrated in 32 patients (20·1 per cent). The incidence of lymph node metastasis in mucosal cancer was 9 per cent and in submucosal cancer 26 per cent.

The surgical procedure was total gastrectomy–R_2 in 68 patients (42·8 per cent) and subtotal gastrectomy–$R_{0/1}$ in 91 (57·2 per cent). The operative mortality rate was 4·4 per cent (seven patients): three deaths occurred after total gastrectomy–R_2 and four after subtotal gastrectomy–$R_{0/1}$. Of the 159 patients with EGC, 128 were alive at the end of follow-up, an overall crude survival rate of 80·5 per cent.

Death was from recurrence of gastric cancer in 11 patients and other causes in 13. In the former group, three deaths occurred after total gastrectomy–R_2 (one hepatic and lymph node recurrence, one hepatic metastasis, one peritoneal dissemination) and eight after subtotal gastrectomy–$R_{0/1}$ (four gastric remnant recurrence, two hepatic metastasis, one lymph node metastasis and peritoneal dissemination, one peritoneal dissemination alone). In the latter group, three deaths were recorded after total gastrectomy–R_2 (one myocardial infarction, one primary breast cancer, one car accident) and ten after subtotal gastrectomy–$R_{0/1}$ (two primary lung cancer, three primary colonic cancer, one myocardial infarction, three pneumonia, one sepsis). One patient in the group undergoing subtotal gastrectomy–$R_{0/1}$ was alive with gastric remnant recurrence 3 years after the initial operation at the time of follow-up.

Table 1 *Univariate analysis of eight factors related to the prognosis of early gastric cancer based on the Kaplan–Meier method*

	No.	Deaths	Survival rate (%)		*P**	Estimated relative hazard (95% confidence interval)
			5 years	10 years		
Sex						
M	89	18	82	76	0·82	1·00†
F	70	13	83	78		0·90 (0·02–38·46)
Age (years)						
$\leqslant 50$	48	3	96	91	0·02	1·00†
51–57	56	14	76	70		5·05 (1·32–19·19)
$\geqslant 58$	55	14	77	72		4·97 (1·31–18·86)
Depth of invasion						
Mucosal	55	5	92	88	0·02	1·00†
Submucosal	104	26	78	72		3·18 (1·11–19·19)
Histological type						
Intestinal	86	10	80	70	0·07	1·00†
Non-intestinal	73	21	85	85		0·49 (0·20–1·23)
Lymph node metastasis						
Negative	127	20	85	82	0·05	1·00†
Positive	32	11	75	63		2·55 (1·01–6·45)
Macroscopic type						
Ulcerated	112	19	84	81	0·23	1·00†
Non-ulcerated	47	12	80	68		0·61 (0·23–1·61)
Location						
Antrum	69	14	82	76	0·75	1·00†
Body	62	13	83	75		0·62 (0·09–4·25)
Upper third	28	4	84	84		0·95 (0·29–3·07)
Type of surgery						
Total gastrectomy‡	68	9	88	86	0·08	1·00†
Subtotal gastrectomy§	91	22	79	71		1·78 (0·64–5·00)

*Log rank test; †reference category. ‡With lymphadenectomy involving gastric and perigastric nodes (R_2); §with incomplete dissection of gastric and perigastric nodes ($R_{0/1}$)

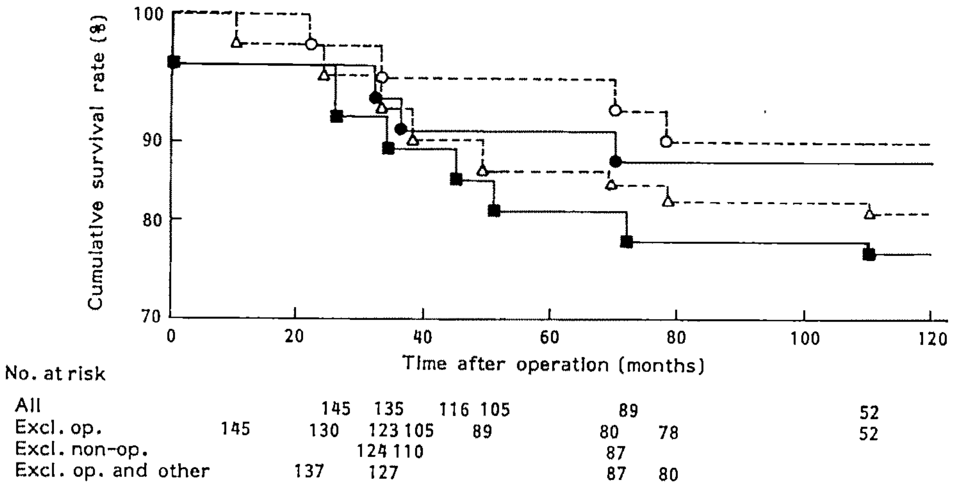

Figure 1 *Cumulative 10-year survival:* ■, *all patients* (n = *159*); △, *excluding operative deaths* (n = *152*); ●, *excluding deaths from other causes* (n = *146*); ○, *excluding operative deaths and those from other causes* (n = *139*)

Table 2 *Factors influencing the effect on survival of the other concomitant variables: Cox proportional hazards model, stepwise analysis adjusted for depth of invasion*

	Risk estimate (95% confidence interval)
Age	2·34 (1·17–4·69)
Histological type	4·48 (1·25–16·09)

Global χ^2 = 14·10, 3 d.f., P = 0·002

Table 3 *Determination of risk ratios for each significant variable*

	Relative risk			
	Favourable	Unfavourable	Risk ratio	P
Age	0·42	2·34	5·57	0·01
Histological type	0·47	2·11	4·49	0·01

Table 4 *Hazard ratio test for age and histological type*

Pattern		
Age (years)	Histological type	Mortality risk*
≤50	Non-intestinal	0·20
≤50	Intestinal	0·90
51–57	Non-intestinal	0·47
51–57	Intestinal	2·11
≥58	Non-intestinal	1·10
≥58	Intestinal	4·96

*Hazard ratio = $\exp\left[\sum_{K=1}^{n} \beta_k (X_{ik} - \bar{X})\right]$

Cumulative 10-year survival rates(s.e.) of the present series (*Figure 1*) were 77·3(3·7) per cent for the whole group (n = 159), 80·9(3·6) per cent excluding operative deaths (n = 152), 86·3(3·0) per cent excluding deaths from other causes (n = 146) and 90·6(2·7) per cent excluding both operative and other mortality (n = 139).

Results of the univariate analysis concerning the prognostic significance of the eight selected factors are shown in *Table 1*. The log rank test showed three factors to be significantly related to prognosis: age, depth of tumour invasion and lymph node metastasis. Results of multivariate analysis using the Cox proportional hazards model indicated that none of the variables was significant in the full multivariate model. Stepwise analysis with the same model (*Table 2*) isolated two factors that influenced the effects of the others on survival: histological type and age. Reliability of this model was verified by the global χ^2 value (P = 0·002). The ratios of risks for these two factors are shown in *Table 3* and the hazard ratios for different risk patterns derived from the combination of these factors in *Table 4*.

Discussion

The percentage of gastric cancers diagnosed as early is lower in western countries than in Japan. The reasons for this are generally related to differences in the incidence of gastric cancer and in the use of screening in Japan. The rate of correct preoperative diagnosis by endoscopy and radiology is lower in western centres[20] than in Japan[21]. In Italy, as in other western countries, an improving trend has, however, begun in relation to detection of EGC and surveillance of high-risk groups using endoscopy. The difference in detection rates of EGC between western countries and Japan could be due to differences in clinical and pathological features. No significant age difference was detected between the present patients and those in Japan[22]. In contrast, the mean age of patients with EGC in Northern Europe[23] and the USA[2] is almost 10 years higher than in Japan.

The male:female ratio, location, macroscopic and microscopic types, percentage of operative deaths and recurrences were also similar in the present patients and those in Japan.

The proportion of EGC detected at the mucosal stage in the present series (34·6 per cent) is significantly lower than those given in Japanese reports[22,24–27] and in other western series[28,29], but is similar to values in North American studies[2,30]. This is probably the result of differences in screening programmes.

The proportion of lymph node metastasis (20·1 per cent) was high in the present cohort compared with the majority of published series. Similar rates have been detected only by authors performing $R_{2/3}$ lymphadenectomy[22,31,32], as in 42·8 per cent of the present 159 cases. A further relevant difference is represented by the high percentage of total gastrectomies performed in the present series, which reflects our curative criteria for gastric cancer[33].

The 10-year survival rate of the present patients was not significantly different from those reported in several Japanese series[25–27,34,35] either excluding operative and other causes of death or in evaluation of crude survival. There are two main factors correlated with this result: the low operative mortality rate of 4·4 per cent and the low recurrence rate of 7·9 per cent.

Univariate analysis showed that age and depth of tumour invasion are factors strongly related to survival (P < 0·02). The presence of lymph node metastasis has lesser significance (P < 0·05). Similar findings were reported by Yasuna and Hayashi[27] for age, by Kitaoka *et al.*[34] for depth of invasion and by Habu and colleagues[26] for lymph node metastasis. Patients with EGC treated by subtotal gastrectomy–$R_{0/1}$ showed a slightly lower survival rate than those undergoing total gastrectomy–R_2, but the difference was not significant. This result, similar to that reported by Raab *et al.*[28], seems to be due to four cases of gastric remnant recurrence but, according to Boku and colleagues[31], could also be related to inadequate lymph node dissection. The possibility of gastric remnant relapse suggests that there may be value in intraoperative examination of the resection margin and that the indications for total gastrectomy–R_2 could be extended. Complete R_2 lymph node dissection with subtotal gastrectomy can be dangerous when the cancer is located in the body with or without invasion of the antrum. Lymph node dissection along the splenic artery (JRSGC n2 group 11) and at the splenic hilum (JRSGC n2 group 10) requires the interruption of both the posterior gastric artery and the short gastric vessels, with a risk of ischaemia for the gastric remnant. The remaining blood supply from the left subphrenic artery may be interrupted or insufficient, leading to ischaemia of the gastric remnant[36].

The better survival rate for the non-intestinal histological type in comparison with the intestinal type confirms data reported by Japanese authors[37–39]. Because all prognostic variables interact, multivariate analysis was used (*Table 2*). After stepwise analysis, the Cox proportional hazards model showed that histological type and age are the factors influencing the effect on survival of the other variables examined after adjusting for depth of invasion. The relative importance of age and histology was clarified by the high risk ratios (*Table 3*).

Finally, the hazards ratio identified the combinations of these two factors associated with the risk of death (*Table 4*). For example, a patient aged $\geqslant 58$ years with an EGC of intestinal histological type has a risk of death 24·8 (4·96/0·20) times greater than that of a patient of $\leqslant 50$ years with non-intestinal type cancer. Increased age was associated with increased risk of a fatal outcome, but at all ages intestinal-type histology showed four to five times greater risk than the non-intestinal type.

In conclusion, the results of this analysis on factors influencing the long-term survival after surgical treatment of EGC are sufficient to detect only a gross trend; however, they show a significant dominance of host- and tumour-related factors (age and histological type) over the type of surgical procedure performed.

References

1. Maruyama K. The general rule of JRSGC and treatment results by the rule. *Cancer Lett* 1989; **45**: 155.
2. Lehnert T, Sternberg SS, Sprossmann M, De Cosse J. Early gastric cancer. *Am J Surg* 1989; **157**: 202–7.
3. Heberer G, Teichmann RK, Kramling H-J, Gunther B. Results of gastric resection for carcinoma of the stomach: the European experience. *World J Surg* 1988; **12**: 374–81.
4. Crespi M. Italian survey of early gastric cancer. *Cancer Lett* 1988; **39**: 7.
5. Hiki Y, Shimao J, Yamao Y *et al.* The concepts, procedures, and problems related to endoscopic laser therapy of early gastric cancer. *Surg Endosc* 1989; **3**: 1–6.
6. Imaoka W, Ida K, Katoh T, Okuda J, Kawai K. Is curative endoscopic treatment of early gastric cancer possible? *Endoscopy* 1987; **19**(Suppl 1): 7–11.
7. Oguro Y, Hirashima T, Tajiri H *et al.* Endoscopic treatment of early gastric cancer: polypectomy and laser treatment. *Jpn J Clin Oncol* 1987; **14**: 271–82.
8. Rösch W, Frühmorgen P. Endoscopic treatment of precancerous and early gastric carcinoma. *Endoscopy* 1980; **12**: 109–13.
9. Yasuda K, Kiyota K, Nakajima M, Kawai K. Fundamentals of endoscopic laser therapy (ELT) for GI tumors – new aspects with endoscopic ultrasonography. *Endoscopy* 1987; **19**(Suppl 1): 2–6.
10. Inberg MV, Heinonen R, Laurén P, Rantakokko V, Viikari S. Total and proximal gastrectomy in the treatment of gastric carcinoma: a series of 305 cases. *World J Surg* 1981; **5**: 249–55.
11. Papachristou DN, Fortner JG. Adenocarcinoma of the gastric cardia: the choice of gastrectomy. *Ann Surg* 1980; **192**: 58–64.
12. De Calan L, Portier G, Ozoux JP, Rvallain B, Perrier M, Brizon J. Carcinoma of the cardia and proximal third of the stomach: results of surgical treatment in 91 consecutive patients. *Am J Surg* 1988; **155**: 481–5.
13. Japanese Research Society for Gastric Cancer. The general rules for gastric cancer study in surgery. *Jpn J Surg* 1973; **3**: 1–71.
14. Japanese Research Society for Gastric Cancer. *General Rules for the Gastric Cancer Study in Surgery and Pathology*. 11th ed. Tokyo: Kanehara Shuppan, 1985.
15. Laurén P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal type carcinoma. *Acta Pathol Microbiol Scand* 1965; **65**: 31–41.
16. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–81.
17. Lee ET. *Statistical Methods for Survival Data Analysis*. Belmont, Massachusetts: Lifetime Learning Publications, 1980.
18. Mantel N. Evaluation of survival data and two new rank-order statistics arising in its consideration. *Cancer Chemother Rep* 1966; **50**: 163–70.
19. Cox DR. Regression models and life tables. *J R Stat Soc* 1972; **B34**: 187–220.
20. Ballantyne KC, Morris DL, Jones JA, Gregson RH, Hardcastle JG. Accuracy of identification of early gastric cancer. *Br J Surg* 1987; **74**: 618–19.
21. Maruyama M. Comparison of radiology and endoscopy in the diagnosis of gastric cancer. In: Preece PE, Cuschieri A, Wellwood JM, eds. *Cancer of the Stomach*. London: Grune and Stratton, 1986: 123–44.
22. Korenaga D, Haraguchi M, Tsujitani S, Okamura T, Tamada R, Sugimachi K. Clinicopathological features of mucosal carcinoma of the stomach with lymph node metastases in eleven patients. *Br J Surg* 1986; **73**: 431–3.
23. Miller G, Froehlicher P, Kaufmann M, Maeurer W. 10 years' endoscopic diagnosis of early gastric cancer in Europe. *J Cancer Res Clin Oncol* 1979; **93**: 99–107.
24. Fukutomi H, Sakita T. Analysis of early gastric cancer cases collected from major hospitals and institutes in Japan. *Jpn J Clin Oncol* 1984; **14**: 169–79.
25. Itoh H, Oohata Y, Nakamura K, Nagata T, Mibu R, Nakayama F. Complete ten-year postgastrectomy follow-up of early gastric cancer. *Am J Surg* 1989; **158**: 14–16.
26. Habu H, Takeshita K, Sunagawa M, Endo M. Prognostic factors of early gastric cancer: results of long-term follow-up and analysis of recurrent cases. *Jpn J Surg* 1987; **17**: 248–55.
27. Yasuna O, Hayashi S. Factors influencing the postoperative course of 113 patients with early gastric cancer. *Jpn J Clin Oncol* 1986; **16**: 325–34.
28. Raab M, Stutzer H, Walgenbach S, Junginger T. Einfluss der chirurgischen Behandlungsmethode auf die Prognose des Magenfruhkarzinoms. *Helv Chir Acta* 1985; **52**: 237–40.
29. Huguier M, Msika S, Lacaine F, Houry S. Early gastric carcinoma: don't miss it. *Hepatogastroenterology* 1989; **36**: 33–5.
30. Green PHR, O'Toole KM, Slonim D, Wang T, Weg A. Increasing incidence and excellent survival of patients with early gastric cancer: experience in a United States medical center. *Am J Med* 1989; **85**: 658–61.
31. Boku T, Nakane Y, Okusa T *et al.* Strategy for lymphadenectomy of gastric cancer. *Surgery* 1989; **105**: 585–92.
32. Kodama Y, Sugimachi K, Soejima K, Matsusaka T, Inokuchi K. Evaluation of extensive lymph node dissection for carcinoma of the stomach. *World J Surg* 1981; **5**: 241–8.
33. Carboni M, Guadagni S, Catarci M, Gossetti F, Negro P. Surgical treatment of gastric cancer: our elective procedures for desirable curability. In: Reed PI, Carboni M, Johnston BJ, Guadagni S, eds. *New Trends in Gastric Cancer*. London: Kluwer, 1990: 135–50.
34. Kitaoka H, Yoshikawa K, Hirota T, Itabashi M. Surgical treatment of early gastric cancer. *Jpn J Clin Oncol* 1984: **14**: 283–93.
35. Abe S, Ogawa Y, Nagasue N *et al.* Early gastric cancer: results in general hospitals in Japan. *World J Surg* 1984; **8**: 308–14.
36. Schein M, Saadia R. Postoperative gastric ischaemia. *Br J Surg* 1989; **78**: 844–8.
37. Tong-Hua L, Ming-Chang C. Carcinome gastrique primitif. *J Chir (Paris)* 1982; **119**: 105–13.
38. Matsusaka Y, Soejima K, Kodama Y, Saito T, Inokuchi K. Carcinoma of the stomach in young adults. *Jpn J Surg* 1976; **6**: 170–7.
39. Mori M, Sugimachi K, Ohiwa T, Okamura T, Tamura S, Inokuchi K. Early gastric carcinoma in Japanese patients under 30 years of age. *Br J Surg* 1985; **72**: 289–91.

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Short note

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Gastrointestinal surgery in the aged

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The aim of this study was to analyse the specific problems of gastrointestinal surgery in patients ≥75 years of age. Hospital mortality and morbidity were studied according to the degree of emergency and the type of intervention.

Patients and methods

Between 1985 and 1991, 274 gastrointestinal surgical procedures were performed by senior surgeons on patients ≥75 years of age. The group was composed of 180 women and 94 men of mean age 82·1 (range 75–94) years. Surgical intervention within 24 h of admission was considered as an emergency operation (51 patients) and that after 24 h as an elective procedure (223 patients). *Table 1* lists the types of surgical procedure performed. Fourteen patients (5·1 per cent) were treated in the intensive care unit after surgery.

Results

Table 1 shows the postoperative mortality rate calculated on the basis of the whole period of hospital stay, in contrast to the more conventional 30-day operative mortality rate. The mortality rate for emergency procedures was 33 per cent and that for the series overall 12·8 per cent. A large proportion of deaths after elective surgery were among patients with peritoneal carcinomatosis (ten of 18), and in emergency surgery among those with mesenteric infarction or strangulated hernia with intestinal necrosis requiring bowel resection (eight of 17). Excluding these, the mortality rate for all other patients operated on as an emergency was 21 per cent and for those operated on electively 3·8 per cent. Colorectal, general, hepatobiliary, pancreatic and splenic operations had an intermediate rate of mortality but gastric surgery carried a high mortality rate (five of 20 patients); of the five deaths, four were from a perforated peptic ulcer with peritonitis and one followed gastrectomy for carcinoma. The overall morbidity rate was 24·1 per cent; infectious complications occurred in 9·1 per cent of patients. Social reintegration after hospitalization was good; 94·1 per cent of survivors returned to their source of admission.

Discussion

In this series, patients ≥75 years old represented 10·6 per cent of those having gastrointestinal surgery during the study period. The sex distribution was as expected in a modern aged population. The frequency of emergency operations was comparable to that described in the literature[1]. Emergency surgery remained an important risk factor. Many authors have underlined this; the mortality figures quoted vary from 10 to 60 per cent[1–4]. The difference between the mortality rate for strangulated hernia with bowel necrosis (100 per cent) and that for elective hernia repair (zero) shows the point well. In the present series, the mortality rate for patients with widespread neoplasia was high because these terminally ill patients could not be discharged from hospital; alternative methods of investigation may perhaps avoid surgery in such cases. Colorectal surgery carried a high risk, mainly when patients were operated on for intestinal obstruction; aged people withstand infectious complications and suture breakage poorly, and the mortality rate surrounding relaparotomy was high[3,5]. The mortality rate of 10 per cent in this series was comparable to that described by others and this figure should decline in the future with better patient preparation. This is important as the life expectancy of these elderly patients[5] is 5–10 years. Until 1980 hepatobiliary and pancreatic surgery carried a poor prognosis for the aged patient. Since then, following the development of cholangiopancreatography and endoscopic sphincterotomy, the number of choledochotomies performed has declined and the mortality rate now approaches that for the younger population[1,3,6]; the rate of 3 per cent obtained in the present series is slightly lower than other published results[1].

In the future the outcome of gastrointestinal surgery in the elderly should improve with increasing use of elective hernia repair and a general reduction in emergency operations. In widespread neoplasia, alternative methods of investigation may decrease the need for laparotomy.

Table 1 *Surgical intervention and hospital mortality*

Type of intervention	No. of patients	No. of deaths	Mortality rate (%)
Colorectal and perineal surgery			
Colectomy with anastomosis, Hartmann's procedure, colostomy, abdominoperineal excision, anal or perineal resection	94	9	10
General surgery			
Appendicectomy, haemorrhoidectomy, herniorrhaphy, Zenker's operation, LeVeen's operation	76	1	1
Hepatobiliary, pancreatic and splenic surgery			
Cholecystectomy, choledochotomy, splenectomy, hepatic and pancreatic resection	63	2	3
Gastric surgery			
Gastrectomy, gastrorrhaphy, fundoplication	20	5	25
Laparotomy for generalized gastrointestinal carcinomatosis	13	10	77
Laparotomy for mesenteric infarction (4 patients) and small intestine necrosis from strangulated hernia (4 patients)	8	8	100

References

1. Margiotta SJ Jr, Horwitz JR, Willis IH, Wallack MK. Cholecystectomy in the elderly. *Am J Surg* 1988; **156**: 509–12.
2. Clebert HD, Kattner A, Linquist J *et al.* The geriatric patient in surgery. Experience with patients over the age of 85 years. *Ann Chir* 1991; **45**: 566–9.
3. Mendes da Costa P, Allegaert W. Chirurgie de l'octogénaire. Résultats d'une enquête nationale. *Acta Chir Belg* 1983; **83**(Suppl): 1–100.
4. Linn BS, Linn MW, Wallen N. Evaluation of results of surgical procedures in the elderly. *Ann Surg* 1982; **195**: 90–6.
5. Greenburg AG, Salk RP, Pridham D. Influence of age on mortality of colon surgery. *Am J Surg* 1985; **150**: 65–9.
6. Shinagawa N, Mashita K, Jura J. The operative risk factors of cholelithiasis in the elderly. *Surg Today* (*Jpn J Surg*) 1992; **22**: 29–34.

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Splenectomy in human immunodeficiency virus-related thrombocytopenia

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To evaluate the efficacy and safety of splenectomy in patients with human immunodeficiency virus (HIV)-related thrombocytopenia, 30 HIV-infected patients with thrombocytopenia (platelet count $<50 \times 10^9/l$) who underwent splenectomy were followed prospectively for a mean period of 42 months. There were no perioperative deaths and morbidity was minimal. Twenty-one patients had a persistent complete response, six had a partial response and were asymptomatic after splenectomy, and only three showed no response. Three patients developed acquired immune deficiency syndrome during follow-up, an incidence that was no different from that expected. Splenectomy is a safe and effective treatment in HIV-infected patients with severe symptomatic thrombocytopenic purpura resistant to medical therapy.

Since the report of autoimmune thrombocytopenic purpura in homosexual men by Morris *et al.*[1] in 1982, this disease has been reported in patients from all groups at risk of acquired immune deficiency syndrome (AIDS): homosexual men[2], intravenous drug abusers[3] and patients infected through transfusion or heterosexual contact[4]. In the absence of AIDS, the prevalence of thrombocytopenia in human immunodeficiency virus (HIV)-infected individuals ranges from 5 to 15 per cent and is independent of the clinical or immunological status of the patient[5,6]. In most cases the syndrome is clinically indistinguishable from classical idiopathic thrombocytopenic purpura (ITP) but its pathophysiology remains unclear.

Response to prednisone therapy and splenectomy has been evaluated in homosexual men with thrombocytopenia[7]. Results appeared similar to those obtained in ITP. More recently, splenectomy has been recommended as the treatment of choice as a result of encouraging short-term results[8], although others have not found such a good response[9]. None of these series has reported long-term follow-up.

To define this new syndrome, evaluate its place in the natural history of HIV infection and compare different therapeutic approaches, 30 HIV-infected patients with thrombocytopenia (platelet count $<50 \times 10^9/l$) who underwent splenectomy were studied prospectively.

Patients and methods

Thirty HIV-infected patients with thrombocytopenia who underwent splenectomy between February 1984 and September 1990 were studied. Thrombocytopenia was defined as a platelet count $<50 \times 10^9/l$. Diagnosis was confirmed by a normal or increased megakaryocyte count in bone marrow aspirates associated with normal coagulation tests and absence of schistocytes on the blood smear. Platelet-bound immunoglobulin G (IgG) was detected by a quantitative antiglobulin consumption assay. The presence of serum IgG with antiplatelet activity was assayed using indirect immunofluorescence.

All patients received medical treatment in an attempt to increase the platelet count: prednisone 1 mg/kg for 4 weeks (18 patients), danazol 600 mg/day (seven) or zidovudine (AZT) (13). AZT was used prospectively for a median of 24 (range 3–33) months; six patients experienced a significant increase in platelet count, but relapsed.

Splenectomy was considered in patients with symptomatic refractory thrombocytopenia in spite of adequate medical treatment. Asymptomatic thrombocytopenia was not an indication for surgery. Intravenous polyvalent high-dose immunoglobulin (Veinglobulines; Mérieux, Lyons, France) was used before surgery in 22 patients with severe symptomatic thrombocytopenia, in an attempt to avoid the need for postoperative blood product transfusion. No other preoperative treatment was used. All the patients except one received preoperative antipneumococcal vaccination. No platelet transfusions were administered before operation; one patient received a platelet transfusion after surgery for mild postoperative bleeding.

The operation was performed through a midline abdominal incision. All patients were given penicillin G for at least 2 years after operation. Standard response criteria for ITP were adopted to assess response to splenectomy[10]. The effect of splenectomy on the patient's platelet count was categorized as complete, partial or no response. Complete response was defined as a sustained increase in platelet count to $>150 \times 10^9/l$. No response represented a failure of the platelet count to achieve a level of at least $50 \times 10^9/l$.

Results

The clinical data are summarized in *Table 1*. The mean age was 29 (range 17–41) years; there were 26 men and four women. AIDS risk groups were as follows: eight homosexual men, 17 intravenous drug abusers, four transfused patients and one heterosexual. Thrombocytopenia led to diagnosis of HIV infection in 28 patients, whereas in two patients thrombocytopenia was diagnosed during systematic follow-up for HIV infection (2 and 9 months after diagnosis of HIV). All patients had clinical bleeding at the initial evaluation: 28 had increased bruising, petechiae or epistaxis, and two had evidence of mild lower gastrointestinal bleeding. In 16 patients, the syndrome was clinically indistinguishable from classical idiopathic autoimmune thrombocytopenia since thrombocytopenia was the only manifestation of HIV infection. In the other patients, thrombocytopenia was associated with other clinical signs of HIV infection: polyadenopathy in seven patients, splenomegaly in four, and minor infections or constitutional symptoms in three.

The mean value for $CD4^+$ cell count was 465 (range 66–1488) $\times 10^6/l$. Fourteen patients (47 per cent) had $<400 \times 10^6$ $CD4^+$ cells per litre at the time of diagnosis of thrombocytopenia, and four (13 per cent) $<200 \times 10^6/l$. Serum p24 antigen was detectable in six patients (20 per cent). Platelet-bound IgG was detected in 23 cases (77 per cent) and serum antiplatelet IgG in 18 (60 per cent). Co-infection with hepatitis B virus was frequent: only four patients (13 per cent) had a completely negative serology, four (13 per cent) were positive for hepatitis B surface antigen, 21 (70 per cent) for hepatitis B and C surface antibodies, and ten (33 per cent) had mild persistent hepatitis.

The mean interval between the diagnosis of thrombocytopenia and surgery was 7 (range 2–18) months. The mean lowest preoperative platelet count (before immunoglobulin) was 13·5 (range 2–34) $\times 10^9/l$. The mean preoperative platelet count in the group treated with immunoglobulin was 99 (range 48–122) $\times 10^9/l$. The overall mean preoperative platelet count

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Table 1 *Details of 30 patients with human immunodeficiency virus-related thrombocytopenia*

Patient no.	Age (years)	Sex	AIDS risk group	Platelet count (× 10^9/l) Lowest before operation	1 week after operation	At last follow-up	Follow-up (months)
1	24	M	Drug abuser	4	80	94	72
2	30	F	Drug abuser	20	497	378	48
3	25	M	Heterosexual	26	354	5*	47
4	32	M	Transfused	6	110	164	28
5	37	M	Homosexual	5	278	270†	35
6	24	F	Drug abuser	20	400	302	48
7	22	M	Homosexual	19	403	250†	38
8	23	M	Drug abuser	11	537	403	49
9	41	M	Drug abuser	30	211	211	10
10	27	M	Drug abuser	7	262	200	37
11	27	M	Drug abuser	10	114	229	50
12	24	M	Drug abuser	27	162	253	59
13	24	M	Drug abuser	7	341	7	51
14	26	M	Drug abuser	19	223	70	42
15	24	M	Transfused	6	342	210	12
16	25	M	Homosexual	3	190	200	45
17	35	F	Drug abuser	9	410	130	52
18	39	M	Homosexual	2	200	350	53
19	17	M	Transfused	30	317	90	38
20	36	M	Drug abuser	18	178	96	31
21	38	M	Drug abuser	16	254	190	26
22	36	M	Drug abuser	8	532	204	37
23	34	M	Drug abuser	3	278	152	25
24	33	M	Homosexual	8	361	198	68
25	28	F	Drug abuser	15	475	310	49
26	23	M	Homosexual	13	200	215	14
27	36	M	Homosexual	5	544	306	13
28	29	M	Transfused	20	120	81	22
29	33	M	Drug abuser	4	230	20	74
30	25	M	Homosexual	34	620	289	77

AIDS, acquired immune deficiency syndrome. *Died from AIDS; †developed AIDS

was 72 (range 11–122) × 10^9/l. No patient required blood transfusion during or after surgery and there were no intraoperative complications. There were no perioperative deaths and the only major complication was one case of postoperative bleeding from the splenic bed which required operation for haemostasis. Minor complications were fever in 15 patients, wound infection in two and atelectasis in two. The mean hospital stay after operation was 6 (range 4–14) days. The mean splenic weight was 264 (range 115–420) g. In three patients an accessory spleen was found. Histological examination of the spleen showed lymphoid hyperplasia of the white pulp and congestion of the cords and sinuses of the red pulp in 25 patients; the spleen was normal in the remaining five.

Platelet counts 1 week after splenectomy are shown in *Table 1*. Twenty-six of the 30 patients (87 per cent) responded initially to splenectomy with a platelet count > 150 × 10^9/l. The remaining four patients had counts > 50 × 10^9/l. Only two of these had evidence of complete response during the entire follow-up; the remaining two patients maintained a partial response and were asymptomatic. There was no relation between preoperative platelet count and response to splenectomy. Long-term outcome is shown in *Table 2*. The mean follow-up was 42 (range 10–77) months. Twenty-one patients (70 per cent) had a persistent complete response following splenectomy. Two patients developed AIDS 24 and 26 months after splenectomy. Six patients (20 per cent) had a partial response; they were all asymptomatic and required no further medical treatment. Three patients (10 per cent) showed no response. In this group, one patient who did not have antipneumococcal vaccination and who took antibiotic prophylaxis irregularly developed pneumococcal meningitis 15 months after surgery, and recovered. Nevertheless, this patient developed AIDS 4 years after surgery and finally died from toxoplasmosis.

Table 2 *Long-term effect of splenectomy on platelet count*

Follow-up (months)	Patients	Platelet count (× 10^9/l) < 50	50–150	> 150
≤ 12	2	0	0	2
13–36	8	0	2	6*
37–60	16	2†	3	11*
> 60	4	1‡	1	2
Total	30	3	6	21

*One patient alive with acquired immune deficiency syndrome (AIDS); †one patient died from AIDS; ‡complete response for first 2 years

Discussion

The association between thrombocytopenia and HIV infection is now well established. Serological surveys, as well as

Table 3 *Summary of reported series of splenectomy in patients infected with human immunodeficiency virus*

Reference	No. of patients	Mean platelet count before operation ($\times 10^9$/l)	Follow-up (months)	Response		
				None	Partial	Complete
Walsh *et al.*[7]	10	16	10	0	0	10
Ferguson[8]	11	19·7	12	—	11*	—
Tyler *et al.*[9]	8	20·8	13	2	5	1
Abrams *et al.*[11]	15	—	—	5	0	10
Kim *et al.*[12]	4	21	—	0	0	4
Oksenhendler *et al.*[19]	14	8·6	10	4	4	6
Schneider *et al.*[20]	15	24·6	12	0	6	9
Rosenfelt *et al.*[22]	4	—	—	1	1	2
Goldsweig *et al.*[23]	7	11·7	14	2	1	4
Present series	30	13·5	42	3	6	21
Total	118			17	34	67

*Platelet count $> 100 \times 10^9$/l only specified

epidemiological, immunological and virological data, confirm that thrombocytopenia is related to HIV infection[11].

The exact mechanism of development of thrombocytopenia remains unknown. HIV-related thrombocytopenia shows both similarities and differences with classical autoimmune thrombocytopenic purpura. The role of autoantibodies or immune complexes in peripheral platelet destruction is still debated, as well as the possible direct or indirect involvement of HIV itself[3]. The possible role of non-specific immune complexes or complement deposition was first suggested by Walsh *et al.*[2], who compared thrombocytopenia in homosexual men with the classical condition. The homosexual group had 3·8-fold higher levels of platelet-bound IgG. In the present series, platelet-bound IgG was found in 77 per cent of cases; these data confirm the peripheral and immunological mechanism of the platelet destruction. In some instances, the delay between HIV seroconversion and thrombocytopenia can be estimated. The combined analysis of three series[12–14] of haemophiliacs showed that the mean delay before the occurrence of thrombocytopenia was 30 months. In the present limited experience of four HIV-infected transfusion recipients, thrombocytopenia occurred after a mean delay of 32 (range 7–60) months. The presence of detectable serum p24 antigen in 20 per cent of the present patients, polyadenopathy in 23 per cent or CD4$^+$ cell count $<200 \times 10^6$/l in 13 per cent suggests that, although thrombocytopenia occurs mainly in asymptomatic HIV-infected individuals, it often occurs at a relatively late stage of the silent period of infection.

The similarity with classical autoimmune thrombocytopenic purpura led most authors to use corticosteroids as initial therapy[8,15]. The present authors have treated 18 patients with prednisone: only ten (56 per cent) responded initially to therapy, but the increase in platelet count was not sustained after prednisone was stopped. This disappointing response, poor tolerance and the potential risk of increased immune deficiency[16] led to the avoidance of corticosteroids as initial therapy for HIV-related thrombocytopenia. AZT has been used prospectively in 34 HIV-infected patients with severe thrombocytopenia, half of whom had a significant and persistent increase in platelet count[17]. These data allow the conclusion that AZT is probably the treatment of choice for HIV-related thrombocytopenia. Intravenous polyvalent high-dose immunoglobulin therapy is usually effective in the treatment of HIV-related thrombocytopenia, with a rapid but transient effect[18,19]. The present authors generally use this therapy before surgery in patients with severe thrombocytopenia. A course of 1–2 g/kg for 2–5 days usually increases the platelet count[19] to safe levels in 3–8 days.

In the present series the initial response to splenectomy was excellent. The platelet count rose above 150×10^9/l in 87 per cent of patients. Some reports have suggested that splenectomy is an effective procedure with an acceptably low morbidity rate[2,9,20,21]. These reports are summarized in *Table 3*. However, none of these series reported long-term follow-up. In the present series, with a mean follow-up of 42 months, a prolonged complete response was found in 70 per cent of patients. Overall, 27 patients (90 per cent) were asymptomatic after surgery. No preoperative factors were found that could predict the response to splenectomy in HIV-infected patients.

There is a potential risk of severe bacterial infection after splenectomy. One patient, who had no antipneumococcal vaccination and irregular antibiotic prophylaxis, developed pneumococcal meningitis. The present authors recommend systematic antipneumococcal vaccination before splenectomy and oral penicillin for 2 years, or if possible lifelong, after surgery because the effectiveness of the vaccine is uncertain in HIV-infected patients. The overall surgical risk in this population does not seem to be any higher than in patients with ITP. The present authors have not performed splenectomy in patients with documented AIDS, in whom the effects of splenectomy are largely unknown.

The prognostic value of thrombocytopenia is difficult to assess in the absence of a proper control group. Some authors have considered that survival of patients with persistent generalized lymphadenopathy was shorter when thrombocytopenia was present[6,24]. However, taking into account the clinical, immunological and virological characteristics of the patients at the time of diagnosis of thrombocytopenia, the present data were no different from those observed in the general population of HIV-infected patients[25,26]. There is no agreement about the influence of splenectomy on the development of AIDS. One report, with few cases, concluded that splenectomy might accelerate its development[27]. In the present series only three patients developed AIDS; this is no different from the expected incidence of AIDS in infected patients without thrombocytopenia[7,8,12], and we agree with others that splenectomy does not appear to increase the risk of AIDS in patients who are HIV positive[1,11].

The present findings allow recommendations on the management of patients with HIV-related thrombocytopenia. No treatment should be given to patients with no or mild haemorrhagic symptoms and moderate thrombocytopenia. In patients with profound thrombocytopenia, AZT appears to be an effective and safe therapy. Because of its high response rate and the rapidity of the response, high-dose intravenous polyvalent immunoglobulin is the first-line treatment for patients with clinical bleeding and severe thrombocytopenia, and is useful before surgery to obviate the need for postoperative blood product transfusion. Splenectomy appears safe and effective in patients with severe symptomatic AZT-resistant thrombocytopenic purpura.

References

1. Morris L, Distenfeld A, Amorosi E, Karpatkin S. Autoimmune thrombocytopenic purpura in homosexual men. *Ann Intern Med* 1982; **96**: 714–17.
2. Walsh CM, Nardi MA, Karpatkin S. On the mechanism of thrombocytopenic purpura in sexually active homosexual men. *N Engl J Med* 1984; **311**: 635–9.
3. Savona S, Nardi MA, Lennette ET, Karpatkin S. Thrombocytopenic purpura in narcotic addicts. *Ann Intern Med* 1985; **102**: 737–41.
4. Karpatkin S, Nardi MA, Hymes KB. Immunologic thrombocytopenic purpura after heterosexual transmission of human immunodeficiency virus (HIV). *Ann Intern Med* 1988; **109**: 190–3.
5. Cattaneo R, Rossi G, Carella G *et al.* HLA antigens and thrombocytopenia in HIV seropositive subjects. *Br J Haematol* 1988; **68**: 268.
6. Polk BF, Fox R, Brookmeyer R *et al.* Predictors of the acquired immunodeficiency syndrome developing in a cohort of seropositive homosexual men. *N Engl J Med* 1987; **316**: 61–6.
7. Walsh C, Krigel R, Lennette E, Karpatkin S. Thrombocytopenia in homosexual patients: prognosis, response to therapy, and prevalence of antibody to the retrovirus associated with the acquired immunodeficiency syndrome. *Ann Intern Med* 1985; **103**: 542–5.
8. Ferguson CM. Splenectomy for immune thrombocytopenia related to human immunodeficiency virus. *Surg Gynecol Obstet* 1988; **167**: 300–2.
9. Tyler DS, Shaunak S, Bartlett JA, Iglehart JD. HIV-1-associated thrombocytopenia. *Ann Surg* 1990; **211**: 211–17.
10. Pizzuto J, Ambriz R. Therapeutic experience of 924 adults with idiopathic thrombocytopenic purpura: multicentric trial of the cooperative Latin American group on hemostasis and thrombosis. *Blood* 1984; **64**: 1179–83.
11. Abrams DI, Kiprov DD, Goedert JJ. Antibodies to human T-lymphotropic virus type III and development of the acquired immunodeficiency syndrome in homosexual men presenting with immune thrombocytopenia. *Ann Intern Med* 1986; **104**: 47–50.
12. Kim HC, Raska K, Trooskin S, Saidi P. Immune thrombocytopenia in hemophiliacs infected with human immunodeficiency virus and their response to splenectomy. *Arch Intern Med* 1989; **149**: 1685–8.
13. Oksenhendler E, Seligmann M. Trombopénie immunologique associée à l'infection HIV. *Médicine Sciences* 1989; **5**: 220–4.
14. Ragni MV, Bontempo FA, Myers DJ *et al.* Hemorrhagic sequelae of immune thrombocytopenic purpura in human immunodeficiency virus-infected hemophiliacs. *Blood* 1990; **75**: 1267–72.
15. Karpatkin S. Immunologic thrombocytopenic purpura in HIV-seropositive homosexuals, narcotic addicts and hemophiliacs. *Semin Hematol* 1988; **25**: 219–29.
16. Schulhafer EP, Grossman ME, Fagin G, Bell KE. Steroid-induced Kaposi's sarcoma in a patient with pre-AIDS. *Am J Med* 1987; **82**: 313–17.
17. Oksenhendler E, Bierling P, Ferchal F *et al.* Zidovudine for thrombocytopenic purpura related to human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1989; **110**: 365–8.
18. Bussel JB, Haimi JS. Isolated thrombocytopenia in patients infected with HIV: treatment with intravenous gammaglobulin. *Am J Hematol* 1988; **28**: 79–84.
19. Oksenhendler E, Bierling P, Farcet JP *et al.* Response to therapy in 37 patients with HIV-related thrombocytopenic purpura. *Br J Haematol* 1987; **66**: 491–5.
20. Schneider PA, Abrams DI, Rayner AA, Hohn DC. Immunodeficiency-associated thrombocytopenic purpura. *Arch Surg* 1987; **122**: 1175–8.
21. Ravumikar TS, Allen JD, Bothe A Jr, Steele G Jr. Splenectomy. The treatment of choice for human immunodeficiency virus-related immune thrombocytopenia? *Arch Surg* 1989; **124**: 625–8.
22. Rosenfelt FP, Rosenbloom BE, Weinstein IM. Immune thrombocytopenia in homosexual men. *Ann Intern Med* 1986; **104**: 583.
23. Goldsweig HG, Grossman R, William D. Thrombocytopenia in homosexual men. *Am J Hematol* 1986; **21**: 243–7.
24. Gold JWM, Weikel C, Godbold J *et al.* Unexplained persistent lymphadenopathy in homosexual men and the acquired immunodeficiency syndrome. *Medicine* 1985; **64**: 203–13.
25. Moss AR, Bacchetti P, Osmond D *et al.* Seropositivity for HIV and the develoment of AIDS or AIDS-related condition: three-year follow-up of the San Francisco General Hospital cohort. *BMJ* 1988; **296**: 745–50.
26. Moss AR, Bacchetti P. Natural history of HIV infection. *AIDS* 1989; **3**: 55–61.
27. Barbui T, Cortelazzo S, Minetti B *et al.* Does splenectomy enhance risk of AIDS in HIV-positive patients with chronic thrombocytopenia? *Lancet* 1987; ii: 342–3.

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Splenectomy for splenomegaly exceeding 1000 grams: analysis of 47 patients

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Forty-seven patients who underwent splenectomy for splenomegaly $\geqslant 1000$ g were studied retrospectively. There were 29 men and 18 women of mean age 56 (range 19–87) years. Haematological malignancy was the most common disorder (42 patients). The main indications for splenectomy were cytopenia (20 patients), diagnosis (14), initial treatment of leukaemia (eight), pain (four) and spontaneous rupture (one). Thirteen patients underwent an associated surgical procedure. One patient died (mortality rate 2 per cent) and 12 (26 per cent) had postoperative complications. The advantages of splenectomy included histopathological diagnosis in 13 of 14 patients with splenomegaly of unknown origin, effective initial treatment in prolymphocytic and hairy cell leukaemia, definitive relief of pain in all affected patients, and long-term improvement of cytopenia in most.

Splenectomy is performed frequently for diagnostic or therapeutic reasons in haematological disorders. The risks and benefits of this operation for massive splenomegaly have not been analysed widely. This is a retrospective study of 47 cases. Massive splenomegaly is defined by convention as a spleen weighing >1500 g, or about ten times the normal weight[1]. In agreement with Johnson and Deterling[2] and Ly and Albrechtsen[3], we consider that, for splenectomy including ligation of the splenic artery as an initial step, 1000 g is a more realistic limit. The aims of this study were to establish morbidity and mortality rates, and the advantages of splenectomy performed for splenomegaly $\geqslant 1000$ g.

Patients and methods

Between May 1981 and May 1991, 152 patients underwent splenectomy for haematological disease, including 47 with splenomegaly $\geqslant 1000$ g ($27 \geqslant 1500$ g). *Table 1* shows the diagnosis for these 47 patients. There were 29 men and 18 women of mean age 56 (range 19–87) years. The main indications for splenectomy were cytopenia (20 patients) diagnosis (14), initial treatment (eight), pain (four) and rupture (one). Thirty-two patients had cytopenia (*Table 2*).

Midline laparotomy was used in all cases. Thirteen patients (28 per cent) underwent 14 associated operative procedures: cholecystectomy (three patients), cholecystectomy and exploration of the common bile duct (one), colectomy (three), gastro-oesophageal fundoplication (three), adnexectomy (two), hernia repair (one) and appendicectomy (one). Hepatic and lymph node biopsies were routine when the cause of splenomegaly was uncertain. Four accessory spleens were found and excised. In 25 patients, ligation of the splenic artery was used as an initial step in the operation. In 40 patients, an abdominal drain was placed (28 sump drains, 12 closed suction systems).

All spleens were weighed in the pathology department several minutes after excision. The mean spleen weight was 1814 (range 1000–4480) g; the largest spleens were found in patients with myeloid splenomegaly, chronic myeloid leukaemia and non-Hodgkin's lymphoma.

Antibiotic prophylaxis and pneumococcal vaccination were routinely used. Platelets were administered before and during surgery when the count was $<50 \times 10^9$/l.

The χ^2 test was used where applicable for statistical analysis.

Results

One patient with chronic myeloid leukaemia died 3 days after splenectomy for spontaneous rupture. The cause of death was massive postoperative haemorrhage associated with acute respiratory failure. The morbidity rate was high: 12 patients (26 per cent) suffered 14 complications (*Table 3*). One patient was reoperated on for haemorrhage after splenectomy for chronic myeloid leukaemia. A huge haematoma of the splenic bed was removed and the outcome after reoperation was uneventful. Associated surgical procedures increased the morbidity, but compared with splenectomy alone the difference was not statistically significant (*Table 4*). The type of haematological disease was not related to the nature and severity of operative morbidity, except there was a higher risk of haemorrhage in myeloproliferative disorders (two of five patients). The mean volume of blood transfused during surgery (excluding the spontaneous rupture) was 2·4 units where preliminary ligation of the splenic artery was performed and 4·5 units for other patients. This difference was significant ($\chi^2 = 7{\cdot}58$, 1 d.f., $P = 0{\cdot}005$). A histological diagnosis was possible in 13 of 14 patients with splenomegaly of unknown

Table 1 *Diagnosis of 47 patients with splenomegaly $\geqslant 1000$ g*

Diagnosis	No. of patients
Non-Hodgkin's lymphoma	17
Chronic lymphatic leukaemia	11
Hairy cell leukaemia	5
Chronic myeloid leukaemia	3
Myeloid splenomegaly	2
Prolymphocytic leukaemia	2
Sarcoidosis	2
Immunoangioblastic lymphadenopathy	1
Hodgkin's disease	1
Gaucher's disease	1
Haemolytic anaemia	1
Undetermined	1

Table 2 *Types of cytopenia*

Cytopenia	No. of patients
Isolated thrombocytopenia*	12
Pancytopenia	9
Thrombocytopenia and anaemia	6
Isolated anaemia†	3
Thrombocytopenia and leucopenia‡	2
Total	32

*Platelets $<100 \times 10^9$/l; †haemoglobin level <10 g/dl; ‡white blood cell count $<1{\cdot}5 \times 10^9$/l

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Table 3 *Postoperative complications of splenectomy for splenomegaly* $\geq$ *1000 g*

Complication	No.	Outcome
Respiratory	7	Satisfactory
Haemorrhage	2	1 satisfactory; 1 reoperation
Subphrenic abscess*	1	Satisfactory
Pulmonary embolism	1	Satisfactory
Septicaemia	1	Satisfactory
Urinary infection	1	Satisfactory
Pancreatitis	1	Satisfactory
Total	14	

Complications affected 12 patients and arose within 1 month of operation. *Treated by percutaneous ultrasound-guided drainage

Table 4 *Postoperative morbidity for five patients undergoing splenectomy with associated surgical procedures*

Patient no.	Associated procedure	Complication
1	Colectomy	Pulmonary infection
2	Cholecystectomy	Haemorrhage*
3	Cholecystectomy and common bile duct exploration	Pancreatitis
4	Gastro-oesophageal fundoplication	Pleural effusion
5	Adnexectomy	Pulmonary embolism

*Patient underwent reoperation

origin. The undiagnosed patient developed acute leukaemia 3 months after surgery.

Seven patiens were relieved of pain; remission of cytopenia in 30 of 32 patients (94 per cent) was observed within 1 month of surgery. In one patient thrombocytopenia was partially improved; another with non-Hodgkin's lymphoma showed no response. Thrombocytopenia recurred in two patients and anaemia recurred in one. A lack of response or the recurrence of thrombocytopenia were considered bad prognostic signs; the five patients in these categories had an early fatal outcome. No patient suffered further pain or morbidity related to the abdominal drainage.

From May 1981 to December 1991, twenty-five patients (53 per cent) died after a mean survival period of 20 (range 2–52) months. Twenty-one deaths were related to the primary malignancy. The other four were from infection (one viral hepatitis at 5 months after splenectomy, one Gram-negative septicaemia at 4 months) or concomitant cancer (one carcinoma of the bladder and one acute leukaemia, both at 26 months). The mean follow-up for the 22 surviving patients was 38 (range 7–127) months. Three patients were lost to follow-up, at 25, 31 and 52 months. The mean time spent in hospital was 14·5 (range 8–38) days for the 46 surviving patients: 12·4 days for patients without postoperative complication and 20·4 days for those with complication.

Discussion

In Europe and North America massive splenomegaly is generally a consequence of malignant disease. Prognosis is not modified by splenectomy[4–6]. Nevertheless, palliative excision is usually justified because of its potential benefits. The present mortality rate of 2 per cent compares favourably with those in the literature of 0–14·7 per cent; the majority of authors report a rate around 5 per cent[1,2,7–9]. The only postoperative death occurred in a patient with spontaneous rupture, a well known indicator of a poor prognosis[10].

The morbidity rate after splenectomy for massive splenomegaly is high, increased twofold or threefold compared with splenectomy for normal-weight spleens[11–14]. In this series, the morbidity rates were 16 per cent for patients with splenomegaly <1000 g and 26 per cent for those with spleens exceeding this weight. This difference was not statistically significant and there was a satisfactory outcome in almost all complicated cases.

Contrary to some authors[1,15,16], a very limited risk of haemorrhage was found; this risk was greatest in myeloproliferative disorders[17,18]. The present results support those of others that the patient's general condition, rather than spleen weight itself, is the most important factor for evaluation of operative prognosis. Preliminary ligation of the splenic artery is a useful procedure that reduces intraoperative haemorrhage and improves access to perisplenic ligaments and adhesions, which may be a major source of bleeding[1,7]. We have no experience of injection of adrenaline into the splenic artery, a procedure that apparently diminishes 40 per cent of the splenic mass without systemic complication[3,9,19], but prefer to place a drain in the splenic bed in patients with thrombocytopenia or myeloproliferative disorders.

Splenectomy offers a number of advantages: diagnosis of splenomegaly of unknown origin, such that specific treatment can be applied if necessary[1,7,9,20]; therapeutic efficacy in hairy cell and prolymphocytic leukaemia; and pain relief and control of thrombocytopenia, enhancing the quality of life[1,6–9]. This operation is a safe and effective procedure when performed by an experienced team.

References

1. Goldstone J. Splenectomy for massive splenomegaly. *Am J Surg* 1978; **135**: 385–8.
2. Johnson HA, Deterling RA. Massive splenomegaly. *Surg Gynecol Obstet* 1989; **168**: 131–7.
3. Ly B, Albrechtsen D. Therapeutic splenectomy in hematologic disorders: effects and complications in 221 adult patients. *Acta Medica Scandinavica* 1981; **209**: 21–9.
4. Coon WW. Splenectomy for splenomegaly and secondary hypersplenism. *World J Surg* 1985; **9**: 437–43.
5. Schwartz SI, Bernard RP, Adams JT, Bauman AW. Splenectomy for hematologic disorders. *Arch Surg* 1970; **101**: 338–47.
6. Wilson RE, Rosenthal DS, Moloney WC, Osteen RT. Splenectomy for myeloproliferative disorders. *World J Surg* 1985; **9**: 431–6.
7. Bickerstaff KI, Morris PJ. Splenectomy for massive splenomegaly. *Br J Surg* 1987; **74**: 346–9.
8. King DJ, Dawson AA, Thompson WD. Splenectomy in patients with malignant lymphoma presenting with massive splenomegaly. *Eur J Haematol* 1987; **38**: 162–5.
9. Shaw JHF, Clark M. Splenectomy for massive splenomegaly. *Br J Surg* 1989; **76**: 395–7.
10. Ricart O, Clot Ph, Bourstyn E, Richard CA. Rupture 'spontanée' de rate au cours des hémopathies: à propos de 2 cas. *Ann Chir* 1987; **41**: 191–4.
11. Fabri PJ, Metz EN, Nick WV, Zollinger RM. A quarter century with splenectomy: changing concepts. *Arch Surg* 1974; **108**: 569–75.
12. Mitchell A, Morris PJ. Surgery of the spleen. *Clinics in Haematology* 1983; **12**: 565–90.
13. Mitchell A, Morris PJ. Splenectomy for malignant lymphomas. *World J Surg* 1985; **9**: 444–8.
14. Musser G, Lazar G, Hocking W, Busuttil RW. Splenectomy for hematologic disease: the UCLA experience with 306 patients. *Am Surg* 1984; **200**: 40–5.
15. Sharp P, Grace CS, Rozenberg MC, Ham JM. Splenectomy for massive splenomegaly. *Aust N Z J Surg* 1985; **55**: 489–92.
16. Wobbes T, van der Sluis RF, Lubbers EJC. Removal of the massive spleen: a surgical risk? *Am J Surg* 1984; **147**: 800–2.
17. Malmaeus J, Akre T, Adami HO, Hagberg H. Early postoperative course following elective splenectomy in haematological diseases: a high complication rate in patients with myeloproliferative disorders. *Br J Surg* 1986; **73**: 720–3.
18. Morgenstern L. Splenectomy for massive splenomegaly due to myeloid metaplasia. *Am J Surg* 1971; **122**: 288–93.
19. Editorial. Splenectomy for massive splenomegaly. *BMJ* 1979; **ii**: 293–4.
20. Letoquart J-P, Casa C, Grosbois B *et al.* La splénectomie à visée diagnostique. A propos de 38 cas. *Ann Chir* 1990; **44**: 342–7.

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Percutaneous ultrasound-guided drainage of intra-abdominal abscesses

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A retrospective review of 200 patients with intra-abdominal abscesses treated by percutaneous ultrasound-guided drainage is reported. Abscesses were simple in 151 patients (75·5 per cent) and complex in 49 (24·5 per cent). In 12 patients the abscess communicated with the gastrointestinal tract. There were 17 critically ill patients for whom percutaneous drainage was the only therapeutic option possible. The success rate was 94·7 per cent (143 of 151 patients) for simple abscess and 69 per cent (34 of 49) for complex abscess. The overall success rate was 88·5 per cent. The mortality rate was 1·3 per cent (two patients) for simple and 16 per cent (eight patients) for complex abscess. The overall mortality rate was 5·0 per cent. Percutaneous ultrasound-guided drainage should be the initial drainage procedure in patients with a simple abdominal abscess. The presence of a complex abscess should not prevent an attempt at percutaneous catheter drainage, particularly in high-risk patients, although the risk of failure is greater in such cases.

The formation of abdominal abscesses is a continuing and sometimes fatal problem. Diagnosis is often difficult. The introduction of antibiotic therapy and advances in bacteriology and diagnostic techniques have improved the outcome, but mortality rates of 11–35 per cent are still reported[1]. Some patients, if diagnosed early, will respond to diagnostic percutaneous aspiration and effective antibiotic therapy. Nevertheless, most cases require drainage. The wider use of percutaneous drainage guided by ultrasonography or computed tomography (CT) had led to a substantial improvement in prognosis. Percutaneous drainage has become the treatment of choice for the majority of intra-abdominal abscesses and fluid collections. The best results have been achieved for single well defined abscesses without evidence of enteric connection, with no adjacent tumour and no tissue necrosis (simple abscesses). Multiple and/or multiloculated abscesses, those that form a fistula to surrounding organs or bowel and abscesses containing viscous fluid, debris or necrotic material are defined as complex. These were formerly considered to be absolute contraindications to catheter drainage, but are now also treated in this way[2].

This paper reports on the use of percutaneous drainage to treat 200 patients affected by intra-abdominal abscesses. Special attention is paid to complications and to the wider indications for use of percutaneous drainage.

Patients and methods

From January 1985 to February 1991, 243 patients with an intra-abdominal abscess were seen, of whom 200 (82·3 per cent) were treated by percutaneous ultrasound-guided drainage. The mean age of the patients was 56·3 (range 8–82) years. In 151 patients (75·5 per cent) the abscess was simple and in 49 (24·5 per cent) complex. In 12 patients an enteric communication was present. There were 17 critically ill patients for whom percutaneous drainage was the only possible therapy. The abscess was spontaneous or post-traumatic in 117 patients (58·5 per cent) and postoperative in 83 (41·5 per cent). The anatomical site of the abscess is shown in *Table 1*. The size ranged from 2 to 19 (mean 7·8) cm.

Drainage was performed in 28 patients (14·0 per cent) by simple or multiple-needle aspiration followed by injection of antibiotic. A preliminary needle aspiration was performed in all cases to evaluate the characteristics of the aspirated material. Direct insertion of a drainage catheter was performed in 22 patients (11·0 per cent). In 150 (75·0 per cent) the catheter was inserted by a modified Seldinger technique. Simple abscesses were drained using one catheter, whereas multiloculated or multiple abscesses required several catheters. In 105 patients (52·5 per cent) double-lumen sump catheters, size 12–14 Fr, were used (Gastrotop sump-drainage catheter; Angiomed, Karlsruhe, Germany and van Sonnenberg catheter; Medi-tech, Boston, Massachusetts, USA). In 67 per cent, a single-lumen 8–10-Fr catheter was inserted (Gastrotop drainage catheter; Angiomed or APD catheter; Medi-tech).

Table 1 *Anatomical site of 200 intra-abdominal abscesses*

Site	Simple	Complex	Total
Intraperitoneal			
Subphrenic	41 (79)	11 (21)	52
Subhepatic	19 (79)	5 (21)	24
Paracolic gutter–intermesenteric	43 (88)	6 (12)	49
Pelvic	16 (73)	6 (27)	22
Retroperitoneal			
Pancreatic lesser sac	4 (25)	12 (75)	16
Psoas–pararenal	6 (75)	2 (25)	8
Intraparenchymal			
Hepatic	17 (74)	6 (26)	23
Renal	4 (100)	0 (0)	4
Splenic	1 (100)	0 (0)	1
Hepatic and splenic	0 (0)	1 (100)	1
Total	151 (75·5)	49 (24·5)	200

Values in parentheses are percentages

In one patient with multiple liver abscesses, percutaneous ultrasound-guided catheterization of the portal vein was performed for locoregional chemotherapy. The drainage procedure was carried out in the ultrasonography department in 143 patients and in the intensive care unit as a bedside procedure in 57. When there was evidence of a possible fistula with the biliary tree, gastrointestinal tract or pancreatic duct, drainage was performed in association with fluoroscopy. Percutaneous drainage was used as the preferred treatment for simple pancreatic abscesses whereas complex pancreatic abscesses were treated by the procedure only in critically ill patients (APACHE II score > 15) as a temporary measure (*Figure 1*). Drainage was considered to be successful when the patient was cured without further surgical intervention or when such intervention was performed for disease in the absence of a residual abscess (e.g. drainage of sigmoid diverticular abscess).

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Results

The success rate for treatment of simple abscess was 94·7 per cent (143 of 151 patients) and 69 per cent (34 of 49) for complex abscess (*Table 2*). The overall success rate was 88·5 per cent. Catheters were left in place for a mean of 9·8 (range 3–17) days in simple abscesses and, significantly longer, for a mean of 31·8 (range 8–67) days in complex abscesses ($P < 0{\cdot}05$, Student's *t* test). Percutaneous drainage failed in 23 patients (11·5 per cent) for whom surgical drainage was necessary. Multiloculation and the presence of necrotic tissue were the most common causes of failure. Undiagnosed abscesses, in most cases intermesenteric, were found in seven patients at laparotomy.

Peripancreatic abscesses were treated successfully by percutaneous drainage in only seven of 16 patients. The mortality rate for this group was 25 per cent. In contrast, the success rate for retroperitoneal abscesses without peripancreatic involvement was 100 per cent. For simple intraparenchymal abscesses, percutaneous drainage was successful in 20 of 22 patients compared with four of seven with complex abscesses. In only three of 12 patients with an enteric communication to the abscesses was a surgical approach necessary; three patients with a low-output fistula recovered spontaneously after long-term drainage (for 4, 6 and 7 weeks).

The mortality rate was 1·3 per cent (two patients) for simple abscess and 16 per cent (eight patients) for complex abscess (*Table 3*); the overall mortality rate was 5·0 per cent. Three patients died after percutaneous drainage from multisystem organ failure. Two affected by end-stage malignancy died after drainage from progression of the tumour. Five patients died from multisystem organ failure after percutaneous drainage had failed and surgical drainage had been performed.

Eleven complications related to percutaneous drainage were observed in nine patients (morbidity rate 5·5 per cent). Three patients with an abscess in the paracolic gutter developed an enterocutaneous fistula that recovered spontaneously in 8–15 days. An intraparietal haematoma arose after percutaneous drainage in two patients with a pelvic abscess. A mild haemoperitoneum that did not require transfusion was observed in two patients after drainage of hepatic abscesses and in one after drainage of hepatic and splenic abscesses. In three patients percutaneous drainage was complicated by infection of the abdominal wall at the site of insertion of the catheter.

Table 2 *Success rate for percutaneous drainage*

Site	Simple	Complex	Total
Intraperitoneal			
Subphrenic	40 of 41 (98)	10 of 11 (91)	50 of 52 (96)
Subhepatic	18 of 19 (95)	5 of 5 (100)	23 of 24 (96)
Paracolic gutter–intermesenteric	41 of 43 (95)	4 of 6 (67)	45 of 49 (92)
Pelvic	15 of 16 (94)	5 of 6 (83)	20 of 22 (91)
Retroperitoneal			
Pancreatic lesser sac	3 of 4 (75)	4 of 12 (33)	7 of 16 (44)
Psoas–pararenal	6 of 6 (100)	2 of 2 (100)	8 of 8 (100)
Intraparenchymal			
Hepatic	15 of 17 (88)	3 of 6 (50)	18 of 23 (78)
Renal	4 of 4 (100)	—	4 of 4 (100)
Splenic	1 of 1 (100)	—	1 of 1 (100)
Hepatic and splenic	—	1 of 1 (100)	1 of 1 (100)
Total	143 of 151 (94·7)	34 of 49 (69)	177 of 200 (88·5)

Values in parentheses are percentages

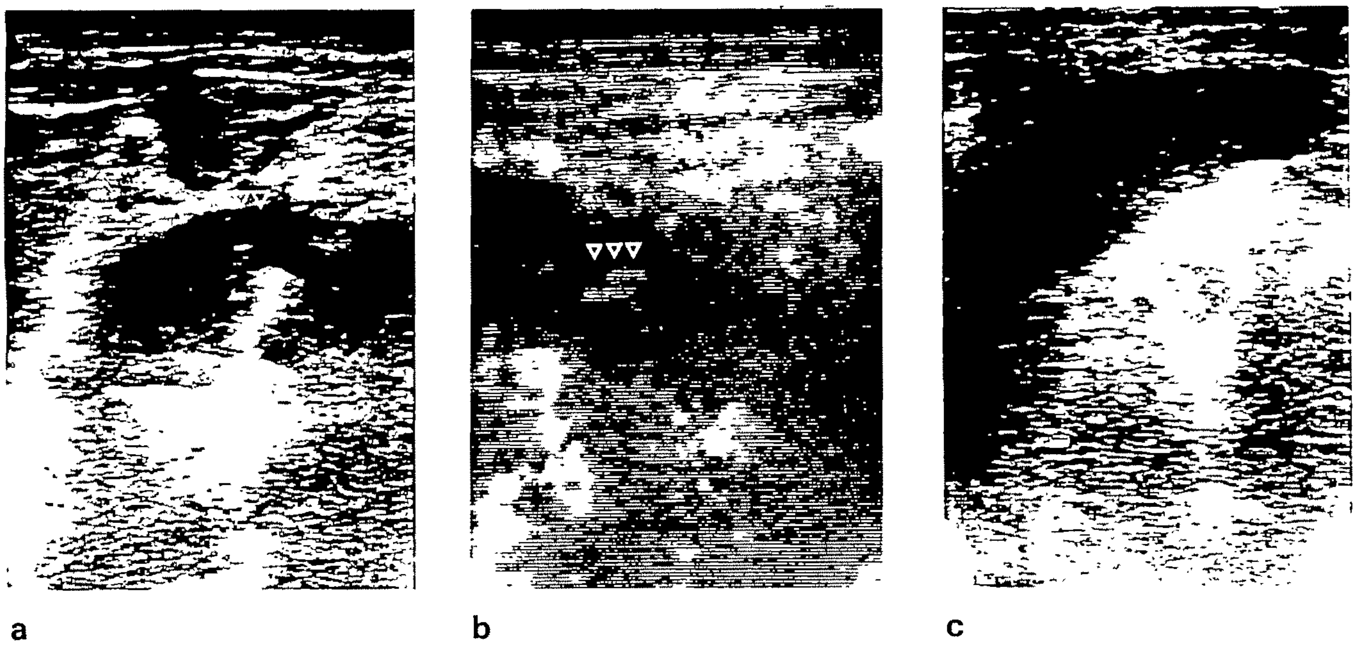

Figure 1 *Percutaneous ultrasound-guided drainage of a peripancreatic retrogastric multiloculated abscess. The abscess is shown* **a** *before treatment (arrows) and* **b** *with a catheter in place (arrows). An additional catheter was required to complete treatment;* **c** *after 10 days of drainage the abscess has completely resolved*

Table 3 *Mortality after percutaneous drainage*

Site	Simple	Complex	Total
Intraperitoneal			
Subphrenic	1 of 41 (2)	1 of 11 (9)	2 of 52 (4)
Subhepatic	0 of 19 (0)	0 of 5 (0)	0 of 24 (0)
Paracolic gutter–intermesenteric	0 of 43 (0)	2 of 6 (33)	2 of 49 (4)
Pelvic	0 of 16 (0)	1 of 6 (17)	1 of 22 (4)
Retroperitoneal			
Pancreatic lesser sac	0 of 4 (0)	4 of 12 (33)	4 of 16 (25)
Psoas–pararenal	0 of 6 (0)	0 of 2 (0)	0 of 8 (0)
Intraparenchymal			
Hepatic	1 of 17 (6)	0 of 6 (0)	1 of 23 (4)
Renal	0 of 4 (0)	—	0 of 4 (0)
Splenic	0 of 1 (0)	—	0 of 1 (0)
Hepatic and splenic	—	0 of 1 (0)	0 of 1 (0)
Total	2 of 151 (1·3)	8 of 49 (16)	10 of 200 (5·0)

Values in parentheses are percentages

Discussion

The prognosis of abdominal abscesses depends on their size, site and number, and the pathogenesis of the fluid collections[3]. Unfavourable prognostic factors include a poor general condition, a history of diffuse peritonitis and a past history of surgery. Several studies have reported mortality rates ranging from 11 to 35 per cent for patients undergoing surgical drainage of abscess[1]. In the authors' experience of surgical drainage of 132 abdominal abscesses over a 10-year period, the overall mortality rate was 13 per cent. The mortality rate for different anatomical sites was nil for retroperitoneal (excluding pancreatic) and intraparenchymal abscess, 2 per cent for periappendiceal and pelvic sites, 25 per cent for other intraperitoneal locations and 50 per cent for pancreatic abscess[4].

The development of new diagnostic methods (ultrasonography, CT) often allows an early diagnosis to be made; overall diagnostic accuracy ranges between 80 and 100 per cent for CT and between 67 and 80 per cent for ultrasonography, depending on the site of collection and experience of the operator[1,4,5].

Recently, percutaneous drainage guided by ultrasonography or CT has been used extensively in the treatment of abdominal abscess as a logical extension of these diagnostic methods[6]. Randomized controlled studies comparing percutaneous and surgical drainage are not available. In a retrospective case–control study no significant difference in morbidity and mortality rate was found between 27 patients with percutaneously drained and 27 with surgically drained abscesses[7]. These results were confirmed recently in a larger study[8]. Since the prelmininary experiences of Haaga and van Sonnenberg, the indications for percutaneous drainage have been extended[3]. Although 80–100 per cent of patients with a single abscess can be cured using this procedure, only 50 per cent of those with a complex abscess are treated successfully. Nevertheless, surprisingly good results have been obtained (60–100 per cent cure rate) for abscesses communicating with the intestinal lumen, abscesses associated with Crohn's disease[9] and infected pancreatic pseudocysts[10]. The success of percutaneous drainage for treatment of retroperitoneal abscesses depends on the site of the infection. The success rate for treatment of renal and perirenal abscess using percutaneous drainage ranges from 75 to 100 per cent[11,12], but abscesses arising in acute pancreatitis, because of their size and spreading nature, are cured percutaneously even with multiple-catheter drainage in only 40–60 per cent of cases[10,13,14]. For complex pancreatic abscesses, percutaneous drainage was used in the present series to treat critically ill patients only as a temporary measure to obtain an improvement in clinical condition as suggested by Pickelman and Moncada[13]. The present data (33 per cent mortality rate) do not, however, support this approach, and confirm the results of Adams *et al.*[14]. Critically ill patients with a high APACHE II score (> 15) and complex pancreatic abscesses probably require immediate surgical drainage and represent the only group for whom failure of percutaneous drainage might lead to undue delay in surgical exploration.

Despite technical difficulties, the drainage of pelvic abscesses can be performed using an abdominal or endoluminal approach, with a success rate of 80 per cent[14–16]. Treatment of abscesses that arise as a complication of acute sigmoid diverticulitis using percutaneous drainage has been discouraged because standard surgical measures address both the underlying pathological condition and local sepsis. A multistage procedure is required in 20–50 per cent of patients. The use of percutaneous drainage to treat selected cases of diverticular abscess might be able to change a two-stage or multistage procedure into a single surgical operation[17–19]. In our experience, a one-stage sigmoid resection and anastomosis could be performed in nine of 12 patients who underwent percutaneous drainage for peridiverticular abscess. Percutaneous drainage for periappendicular abscess is effective and can avoid a surgical operation for the abscess or simplify potentially difficult surgery[20]; however, in our opinion, a single surgical approach (abscess drainage and appendicectomy) is always preferable, except for very high-risk patients, because the incidence of complications is lower.

Percutaneous drainage has been found to be effective for treatment of intraparenchymal abscesses and carries a low mortality rate, usually 3 or 4 (range 0–13) per cent. The abscess fails to resolve in 10–20 per cent of patients[21,22]. In the present study, one death was recorded among 29 patients affected by intraparenchymal abscess (3 per cent); this death was from tumour progression in a patient with end-stage malignancy. Three of the five cases of failure after drainage of hepatic abscesses were in immunocompromised patients; all recovered after surgical drainage. For a patient with multiple hepatic abscesses, catheterization of the portal vein for locoregional chemotherapy was performed and the patient was discharged in good health 10 days after percutaneous drainage. We believe that the combination of abscess drainage and portal vein catheterization may improve the outcome of percutaneous treatment of complex hepatic abscesses.

Multilocation, a thick abscess wall that does not collapse with drainage, and the presence of necrotic tissue, haematoma or a foreign body were common causes of failure. Nevertheless the most common cause of failure, particularly in intermesenteric and infected pancreatic collections, was incomplete diagnosis (30 per cent of cases), despite the widespread use of CT. Improvement in diagnostic accuracy might be obtained using immunoscintigraphy[23].

Drainage guided by CT is more accurate for treatment of retroperitoneal and pelvic abscesses because of the higher definition of this imaging technique[1,15]. Nevertheless, ultrasonography has the advantage of greater versatility and percutaneous drainage can be performed safely at the patient's bedside, which is of help in the management of critically ill patients and those with sepsis.

In conclusion, the results of the present study and previous reports[1,8,9] show that ultrasound-guided percutaneous drainage of abdominal abscesses is indicated whenever feasible as a safe and relatively atraumatic procedure with few complications and late sequelae. In critically ill patients, percutaneous drainage of complex abscesses, despite the low success rate, often permits clinical improvement with subsequent reduction of postoperative mortality. Ultrasound-guided catheterization of the portal vein may have a useful role in the treatment of multiple liver abscesses.

References

1. Brolin RE, Nosher JR, Leiman S. Percutaneous catheter *vs* open surgical drainage in the treatment of abdominal abscesses. *Ann*

Surg 1984; **105**: 102–6.
2. van Waes PF, Feldberg MA, Mali WP *et al.* Management of loculated abscesses that are difficult to drain: a new approach. *Radiology* 1983; **147**: 57–63.
3. Pruett TL, Simmons RL. Stato attuale del drenaggio percutaneo degli ascessi mediante cateteri. *La Clinica del Nord America* 1989; **21**: 103–21.
4. Cavina E, Chiarugi M, Buccianti P, Goletti O. Ascessi addominali, rassegna e casistica. *Atti: Update in Trauma Surgery.* Rome, 1989: 127–34.
5. Goletti, O, Chiarugi M, Buccianti P *et al.* Ultrasound guided percutaneous drainage of abdominal abscesses. *Journal of Emergency Surgery* 1992; **15**: 149–51.
6. Lameris JS, Bruining HA, Jeekel J. Ultrasound-guided percutaneous drainage of intra-abdominal abscesses. *Br J Surg* 1987; **74**: 620–3.
7. Olak J, Christou V, Stein LA, Casola G, Meakins JL. Operative *vs* percutaneous drainage of intra-abdominal abscesses: comparison of morbidity and mortality. *Arch Surg* 1986; **121**: 141–5.
8. Hemming A, Davis NL, Robins RE. Surgical *versus* percutaneous drainage of intraabdominal abscesses. *Am J Surg* 1991; **161**: 593–5.
9. Lambiase RE, Cronan JJ, Dorfman GS *et al.* Percutaneous drainage of abscesses in patients with Crohn's disease. *AJR Am J Roentgenol* 1988; **128**: 1043.
10. van Sonnenberg E, Wittich GR, Casola G *et al.* Complicated pancreatic inflammatory disease: diagnostic and therapeutic role of interventional radiology. *Radiology* 1985; **155**: 355–60.
11. Deyoe LA, Cronan JJ, Lambiase RE, Dorfman GS. Percutaneous drainage of renal and perirenal abscesses: results in 30 patients. *AJR Am J Roentgenol* 1990; **155**: 81–3.
12. Lang EK. Renal, perirenal and pararenal abscesses: percutaneous drainage. *Radiology* 1990; **174**: 109–13.
13. Pickelman J, Moncada R. The role of percutaneous drainage of infected and noninfected pancreatic pseudocysts: experience in 101 cases. *Radiology* 1987; **170**: 757–61.
14. Adams DB, Harvey TS, Anderson MC. Percutaneous catheter drainage of infected pancreatic and peripancreatic fluid collections. *Arch Surg* 1990; **125**: 1554–7.
15. Gazelle GS, Haaga JR, Stellato TA, Gauderer MWL, Plecha DT. Pelvic abscesses: CT guided transrectal drainage. *Radiology* 1991; **181**: 49–51.
16. Van der Kolk HL. Small deep pelvic abscesses: definition and drainage guided with an endovaginal probe. *Radiology* 1991; **181**: 283–4.
17. Feldberg MAM, Hendriks MJ, van Waes PFGM. Role of CT in diagnosis and management of complications of diverticular disease. *Gastrointest Radiol* 1985; **10**: 370–7.
18. Muller PR, Saini S, Wittemburg J *et al.* Sigmoid diverticular abscesses: percutaneous drainage as an adjunct to surgical resection in 24 cases. *Radiology* 1987; **164**: 321–5.
19. Neff CC, van Sonnenberg E, Casola G *et al.* Diverticular abscesses: percutaneous drainage. *Radiology* 1987; **163**: 15–18.
20. van Sonnenberg E, Wittich GR, Casola G *et al.* Periappendiceal abscesses: percutaneous drainage. *Radiology* 1987; **163**: 23–6.
21. Branum GD, Tyson GS, Branum MA, Meyers WC. Hepatic abscesses. *Ann Surg* 1990; **212**: 655–62.
22. Frey CF, Zhu Y, Suzuki M, Isaji S. Liver abscesses. *Surg Clin North Am* 1989; **69**: 259–71.
23. Molea N, Matteucci F, Goletti O *et al.* Le immunoglobuline umane policlonali marcate con tecnezio 99^m nella diagnosi delle sepsi addominali. *Chirurgia* 1992; **5**: 718–23.

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Repeat liver resection for recurrent colorectal metastases

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Sixteen patients underwent 18 repeat liver resections for recurrence of colorectal hepatic metastases that had been previously resected. Only minor liver resection had been undertaken at the first operation; three were palliative. The second operation was major hepatectomy in ten patients, minor resection in five and orthotopic liver transplantation in one. In one patient, lung metastases were resected before the second operation. One repeat hepatectomy was palliative. After partial liver resection, there were no deaths and complications were observed in six of 15 patients. One patient died 2 weeks after liver transplantation. After the second resection, 2-, 3- and 5-year survival rates were 67, 57 and 30 per cent; the mean survival time was 33 (range 8–93) months. Tumour recurrence was observed in 11 of 14 patients 4–32 (mean 13) months after a second curative liver resection; two patients received a third curative operation for recurrent liver metastases. After the second curative hepatectomy, seven patients died from disease after a mean of 36 (range 14–61) months and seven are currently alive at a mean of 33 (range 8–93) months. Four of these patients are free from disease 26–93 months after resection and three are alive with recurrence. Repeat hepatectomy for recurrent colorectal metastases can prolong survival in selected patients and has low operative risk.

Surgical resection is generally considered the best treatment for resectable colorectal liver metastases. The 5-year survival rate[1–13] is around 25 per cent and ranges from 16 to 45 per cent; few patients with histologically proven unresected liver metastases survive 5 years[14–16]. However, in 60–70 per cent of patients, recurrence is observed in the years or even months after resection[6,8,11,17–22]. Approximately half of these recurrences are located in the liver[8]; 10–55 per cent represent isolated hepatic recurrence[2,4,6,8,9,11,17–25]. Most are diffuse and irresectable, but a small percentage are potentially resectable according to their size, location and relationship to the vascular pedicles.

If repeat hepatectomy for recurrent liver metastases is to be worthwhile it must be determined whether operative risk and postoperative mortality and morbidity rates are increased compared with primary liver resection, and what the long-term results are. Therefore, 16 patients who underwent repeat hepatectomy for colorectal metastases from January 1984 to June 1991 were studied.

Patients and methods

Between May 1970 and June 1991, 189 patients underwent hepatic resection for colorectal liver metastases. Of 181 who underwent curative hepatectomy, 75 (41·4 per cent) developed liver recurrence; this was isolated in 60 cases (80 per cent). Ten patients (13 per cent) underwent a second liver resection for recurrence. Two other patients in whom the first resection was incomplete are also included in this report. In addition, four patients were referred to this department from another hospital for a second hepatectomy; in one of these patients the first liver resection had been incomplete. Thus, a total of 16 patients (12 men, four women; mean age at second hepatectomy 60 (range 36–75) years) underwent repeat liver resection; two each underwent three successive resections (*Table 1*). Overall, 8·7 per cent of the 207 liver resections for colorectal metastases were repeat procedures.

Of these 16, the primary tumours were located in the rectum (eight patients), left colon (six), right colon (one) and transverse colon (one) (*Table 1*). Pathological reports were available for 13; eight primary tumours were Dukes' C and five Dukes' B. Contiguous spread of the primary was present in three cases. The resection of the primary tumour had been considered curative in all cases; margins were free from tumour. Three patients had received adjuvant postoperative radiotherapy.

The first liver metastases were synchronous with the primary cancer in ten patients; these were detected a mean of 11·9 (range 6·9–15·4) months later in six. All patients but one were asymptomatic. In nine patients, the liver metastases were diagnosed during surgery. In one of these patients, the metastases were discovered during reoperation for an anastomotic recurrence 11 months after resection of a rectal cancer (patient 5). Serum levels of tumour markers were raised in five of ten patients for whom such information was available.

Six patients had a solitary liver metastasis and ten multiple hepatic metastases (range 2–10 nodules). The metastases involved the left lobe (three patients), the right lobe (seven) or were bilateral (six). The mean diameter of the largest liver metastasis was 2·9 (range 0·2–6·0) cm. Extrahepatic disease was present in three of the 16 patients; recurrence of the primary tumour (patient 5), contiguous diaphragmatic spread of the liver metastases (patient 3) and associated lung metastases (patient 2).

In eight patients, resection of the liver metastases and primary tumour were performed during the same operation; in the other eight the hepatectomy was separated from the intestinal resection by a mean period of 15·2 (range 1·8–28·2) months. Fifteen patients underwent one or more subsegmental resections (metastasectomies). One patient had a left lateral segmentectomy. In six, a Pringle manoeuvre was used for the first liver resection.

A macroscopically complete resection of all tumour tissue, both in and outwith the liver, was achieved in 13 of the 16 patients; this was considered curative. The margin between the tumour and the cut edge of the liver was ≥ 1 cm in 11 cases and <1 cm in two; five of these patients received adjuvant postoperative systemic chemotherapy.

In patients 2, 7 and 15, in whom gross tumour was left in place, hepatectomy was considered palliative. In patient 2, lung metastases and a contralateral liver metastasis were diagnosed 1 month after the first liver resection. In patients 7 and 15, the resection of liver metastases was planned in two sessions. These three patients received postoperative systemic chemotherapy.

The operative mortality and morbidity rates for the first liver resection were 0 and 6·2 per cent respectively and unrelated to the hepatectomy. The mean inpatient stay was 13·7 (range 9–21) days.

Patients were subsequently submitted to a periodical follow-up programme including physical examination, determination of tumour markers in serum, abdominal computed tomography (CT) and/or ultrasonography, chest radiography and colonoscopy. Asymptomatic liver recurrence in 13 patients was discovered a mean of 15·2 (range

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Table 1 *Details of 16 patients undergoing repeat liver resection*

Patient no.	Sex	Age (years)	Location of primary	First disease-free interval (months)	No. of liver metastases	First resection*	Interval between first and second resections (months)	Second resection	Disease-free interval (months)	Third resection*	Status	Survival after last resection (months)
1	M	64	Rectum	0	3	Left metastasectomy (3)	11	Left lobectomy	8	—	Alive with disease	10
2	M	60	Rectum	0	2	Left metastasectomy (1)†	12	Right lobectomy	6	—	Alive with disease	8
3	M	63	Rectum	7	1	Right metastasectomy (1)	13	Right lobectomy	9	—	Died from disease	14
4	M	57	Rectum	0	1	Left metastasectomy (1)	9	Right trisegmentectomy	7	—	Died from disease	24
5	M	67	Sigmoid	11	1	Left lateral segmentectomy	14	Right lateral segmentectomy	25	—	Died from disease	47
6	F	58	Sigmoid	13	4	Right and left metastasectomy (4)	29	Right lobectomy	26	—	Alive without disease	26
7	M	57	Transverse colon	13	10	Right and left metastasectomy (8)†	25	OLT	0·5	—	Died after operation	0·5
8	M	72	Rectum	0	1	Right metastasectomy (1)	40	Right lobectomy	6	—	Died from disease	15
9	F	56	Sigmoid	15	2	Subsegmentectomy (VI)	13	Left lateral segmentectomy	33	—	Alive without disease	33
10	M	49	Rectum	0	2	Right and left metastasectomy (2)	6	Right trisegmentectomy	26	—	Died from disease	61
11	M	63	Rectum	0	4	Right and left metastasectomy (2)	26	Subsegmentectomy (VII)	32	Segmentectomy (VII–VIII)	Died from disease	24
12	M	59	Rectum	13	2	Segmentectomy (VI–VII)	15	Left lobectomy	7	—	Died from disease	32
13	M	35	Splenic flexure	0	1	Right metastasectomy (1)	11	Right trisegmentectomy	12	Left metastasectomy (I)	Alive without disease	38
14	F	64	Sigmoid	0	1	Right metastasectomy (1)	25	Subsegmentectomy (IV)	93	—	Alive without disease	93
15	M	53	Sigmoid	0	2	Right metastasectomy (1)†	15	Right trisegmentectomy†	0	—	Died from disease	14
16	F	57	Right colon	0	4	Right and left metastasectomy (4)	9	Segmentectomy (VI–VII)	4	—	Alive with disease	9

*Values in parentheses are number of metastases; †palliative resection. OLT, orthotopic liver transplantation

5·2–37·0) months after the first liver resection by ultrasonography. In eight cases, the tumours were solitary; four patients had three or more lesions. The mean diameter of the largest tumour was 4·9 (range 2·5–15·0) cm (data from 15 patients). In the nine patients who had undergone curative resection for unilateral metastases, the liver recurrences were unilateral in seven and bilateral in two cases. These recurrences were located in the same lobe in five patients and in the contralateral lobe in four. One of these recurrences was on the cut edge of a metastasectomy (patient 3).

Before reoperative liver surgery all patients underwent physical examination, colonoscopy, CT of the chest and pelvis, and radionuclide bone scintigraphy. At operation, the abdomen was explored to rule out other irresectable sites of recurrence. Of 15 partial second hepatectomies, ten were major resections (more than three segments according to Couinaud[26]) and five minor. Intraoperative ultrasonography of the liver was used routinely. These partial resections were performed under normothermic ischaemia lasting 16–90 (mean 42·5) min, with either a Pringle manoeuvre alone (nine cases) or complete hepatic vascular exclusion (four). In two cases, the Pringle manoeuvre had to be converted into vascular exclusion because of intraoperative haemorrhage. In three, contiguous spread of the tumour required extension of the liver resection to include the diaphragm and pleura. Tumour thrombi were found in two resected specimens: one in a branch of the right portal vein (patient 5) and one in a bile duct (patient 9).

In three patients who had undergone a palliative first hepatectomy (patients 2, 7 and 15), residual tumours remained stable for 1 year while the patients received systemic chemotherapy. In patient 2, pulmonary metastases were completely resected 2 months before the repeat liver resection; the lung metastasectomy was considered curative. Orthotopic liver transplantation was performed in patient 7 with metastases restricted to the liver. Patient 15 could not undergo complete resection of tumour because of invasion of vessels and portal nodes.

Survival rates after the second and last curative liver resection were calculated according to the Kaplan–Meier method.

Results

There was no operative death after partial liver resection. Reversible complications were observed in six patients: ascites (one), liver failure (one), bile leak (one), respiratory complications (three) and thrombophlebitis (one). Adhesions in four patients and trauma to the right hepatic vein in one were responsible for major peroperative haemorrhage. The mean volume of overall replacement of blood loss was 5·7 (range 0–19) units packed red blood cells and 7·3 (range 0–25) units fresh frozen plasma. Five patients did not receive either red blood cells or fresh frozen plasma. The mean inpatient stay was 14 (range 9–23) days. One death occurred on the 16th day after surgery, following liver transplantation.

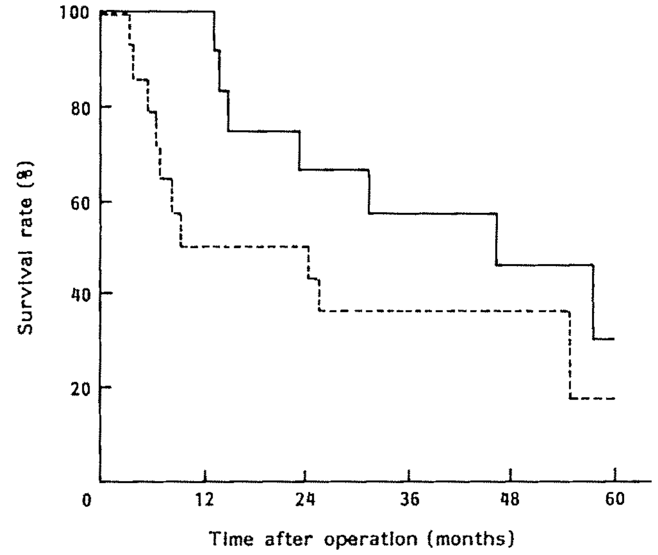

Figure 1 *Overall (—, n = 15) and disease-free (---, n = 14) survival after second liver resection*

Six patients received postoperative systemic chemotherapy.

After the second hepatectomy, the mean follow-up was 33 (range 8–93) months; no patient was lost to follow-up. The 2-, 3- and 5-year overall and disease-free survival rates were 67, 57 and 30 per cent, and 50, 36 and 18 per cent respectively (*Figure 1*). After a second curative liver resection, three patients were free from disease and are currently alive at 26, 33 and 93 months, and 11 presented with recurrence after a mean interval of 13 (range 4–32) months. Recurrent tumour was located in the liver only (six patients), the lungs only (one), the pelvis only (one), the liver and lungs (two), and the lungs and bone (one). Two of eight hepatic recurrences were located on the cut edge of the second liver resection. After the only palliative hepatectomy, patient 15 became jaundiced after 4·6 months and died at 14 months.

Of the six patients with isolated hepatic recurrence, three had diffuse involvement of the liver remnant and the other three could undergo reoperation. One (patient 5) underwent exploratory laparotomy because the projected resection was assumed to be too extensive with regard to the predicted remaining parenchyma. Two patients had a third minor curative hepatectomy, extended to the adjacent diaphragm in one; there was no operative mortality. One patient had transient jaundice and the other a respiratory complication. One (patient 11) showed recurrence on the cut edge of the liver and in aortoiliac nodes 21 months after the third liver resection and died 3 months later. The other (patient 13) is currently alive without disease 38 months after the third hepatectomy.

After the last liver resection, the mean follow-up was 30 (range 8–93) months. No patient was lost to follow-up. The 2-, 3- and 5-year overall and disease-free survival rates were 67, 49 and 32 per cent, and 43, 29 and 29 per cent respectively (*Figure 2*). No liver recurrence was observed in seven of 14 patients after 16 curative resections. Four of these patients are currently alive without disease 26, 33, 38 and 93 months after the last hepatectomy. Seven died from recurrence a mean of 31 (range 14–61) months after the last curative liver resection (*Table 1*).

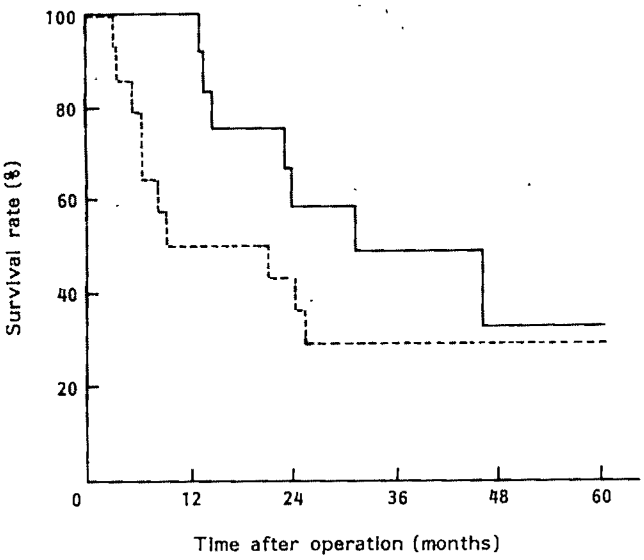

Figure 2 *Overall (—, n = 15) and disease-free (---, n = 14) survival after final liver resection*

Discussion

This report analyses a large series of repeat hepatic resections for recurrent colorectal liver metastases performed in a single institution. Of 181 patients who underwent supposedly curative hepatectomy for colorectal metastases, 41·4 per cent developed liver recurrence and only ten could undergo repeat resection with curative intent. Two patients who had undergone incomplete resection of the first liver metastasis and four referred from another institution were also included in the present series. Operative mortality and morbidity rates were similar for primary and repeat hepatectomy. The 2-, 3- and 5-year survival rates after the second liver resection were 67, 57 and 30 per cent respectively, similar to those observed after primary resection[11]. Four patients are alive and free from disease 26–93 months after the second hepatectomy.

Most recurrences in the liver after resection of hepatic metastases are not resectable. The resectability rate in the present series was 13 per cent; the other recurrences were either multifocal or associated with irresectable extrahepatic recurrence. Resectability rates up to 53 per cent have been observed for recurrent liver metastases[11,21,27–29]. It is reasonable to wait at least a few weeks after diagnosis before resecting a recurrent liver metastasis, to be sure that it is not the first manifestation of diffuse metastatic disease.

In the present series, resectable recurrent liver metastases were observed in patients in whom the first such metastases had been excised with a minor hepatectomy. It could be argued that the first liver resection had been insufficient. The rate of recurrence does not however appear to correlate with the extent of hepatectomy provided a 1-cm margin of normal parenchyma is resected with the tumour[4,5,7,9,10,16,18,30,31]. On the other hand, the rate of repeat hepatic resection for recurrent liver metastases is probably higher after minor hepatectomy because such resections do not greatly modify the anatomy of the organ and do not induce many adhesions, so subsequent liver

Table 2 *Reported cases of repeat hepatectomy for colorectal liver metastases*

Reference	Year	No. of patients	Operative mortality*	Mean interval between resections (months)†	Patients with recurrence*	Deaths*	Mean survival after last resection (months)†
Tomas de la Vega *et al.*[42]	1984	4	0	—	2 (50)	2 (50)	22
Butler *et al.*[2]	1986	2	0	—	0 (0)	0 (0)	6, 17**
Joyeux *et al.*[40]	1987	4	0	—	4 (100)	0 (0)	21 (12–36)
Dagradi *et al.*[27]	1987	9	0	21 (8–38)¶	—	4 (44·5)	16 (1–37)
Nordlinger *et al.*[11]	1987	6	0	18 (5–40)¶	4 (67)	1 (17)	14 (2–28)
Fortner[21]	1988	3§	0	—	2 (67)	1 (33)	5, 16, 39**
Lange *et al.*[33]	1989	9§	0	15 (6–36)	4 (44)	4 (44)	17 (1–41)
Griffith *et al.*[39]	1990	9	1 (11)	21 (1–39)	1 (12)	0 (0)	30 (9–67)
Huguet *et al.*[38]	1990	8	0	17 (6–40)	6 (75)	3 (37·5)	32 (13–56)
Stone *et al.*[28]	1990	10	0	9 (0–20)¶	7 (70)	4 (40)	21 (6–43)
Scheele *et al.*[13]	1991	9	0	—	0 (0)	2 (22)	—
Vogt *et al.*[29]	1991	7♯	0	—	4 (57)	2 (29)	44‡
Gouillat *et al.*[34]	1991	7	0	19 (9–45)	—	—	14‡
Bozzetti *et al.*[23]	1992	11	1 (9)	19 (8–59)	5 (50)	3 (30)	18 (3–42)

*Values in parentheses are percentages; †values in parentheses are ranges; ‡median. §One patient underwent three resections; ♯two patients underwent three resections; ¶disease-free interval; **individual survival times resection is not complicated[32,33]. A second liver resection is also possible after major hepatectomy in some cases[28,33,34]. In such patients, where the anatomy has been modified by liver regeneration, intraoperative ultrasonography of the liver[35] and operative cholangiography can be useful to localize the tumour, detect unsuspected nodules and define their relation with the main vessels and bile ducts.

Clamping of the portal triad can be of particular value in such cases to reduce blood loss during resection. It can be associated with complete hepatic vascular exclusion for the resection of large or posterior liver tumours[36–38]. These techniques are well suited to reduce intraoperative blood loss, now known to be the major determinant of operative mortality and morbidity[25,36]. In the present series, mean blood loss replacement was 5·7 units red blood cells and 7·3 units fresh frozen plasma; five of 15 patients received no blood. No patient died after partial liver resection, and reversible complications were observed in six of 15. The rate of operative death or complication and the mean inpatient stay do not appear to be higher for repeat liver resection[2,11,13,21,27–29,33,34,38–42] (*Table 2*) than for primary hepatectomy[2,3,5,6,9,11,18,24,25,30,31,42–45]. An increased operative mortality rate would certainly reduce or even remove the long-term benefit expected after such resection.

With a mean survival time of 33 months in the present report and 11·5–31·5 months in the literature[2,11,21,27,28,33,38,39,42], the long-term results of repeat hepatectomy are similar to those observed after primary resection. Others[29,34] have observed median survival times after the last liver resection of 44 and 14 months. In six patients undergoing eight liver resections, Nakamura *et al.*[41] observed 2-, 3- and 5-year survival rates after initial hepatectomy of 83, 67 and 50 per cent. The indications to resect recurrent liver metastases should be the same as for first metastases: the tumours should be resected completely with a margin of 1 cm of normal parenchyma if there is no uncontrolled extrahepatic disease and in the absence of portal or coeliac node invasion.

Liver transplantation for diffuse or recurrent hepatic metastases of colorectal cancer is usually followed by rapid recurrence and is not considered worthwhile[46]. For irresectable recurrent liver metastases, cryosurgery has been introduced recently[28].

The present results emphasize the need for careful follow-up after hepatectomy for colorectal metastases to detect resectable liver recurrence. Repeat curative hepatectomy is able to provide prolonged survival in selected patients, with an operative risk similar to that of first procedures.

References

1. Adson MA, Van Heerden JA, Adson MH, Wagner JS, Ilstrup DM. Resection of hepatic metastases from colorectal cancer. *Arch Surg* 1984; **119**: 647–51.
2. Butler J, Attiyeh FF, Daly JM. Hepatic resection for metastases of the colon and rectum. *Surg Gynecol Obstet* 1986; **162**: 109–13.
3. Cobourn CS, Makowka L, Langer B, Taylor BR, Falk RE. Examination of patient selection and outcome for hepatic resection for metastatic disease. *Surg Gynecol Obstet* 1987; **165**: 239–46.
4. Doci R, Gennari L, Bignami P, Montalto F, Morabito A, Bozzetti F. One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinants. *Br J Surg* 1991; **78**: 797–801.
5. Ekberg H, Tranberg KG, Andersson R *et al.* Determinants of survival in liver resection for colorectal secondaries. *Br J Surg* 1986; **73**: 727–31.
6. Fortner JG, Silva JS, Golbey RB, Cox EB, MacLean J. Multivariate analysis of a personal series of 247 consecutive patients with liver metastases from colorectal cancer. I. Treatment by hepatic resection. *Ann Surg* 1984; **199**: 306–16.
7. Holm A, Bradley E, Aldrete JS. Hepatic resection of metastasis from colorectal carcinoma – morbidity, mortality, and pattern of recurrence. *Ann Surg* 1990; **209**: 428–34.
8. Hughes KS, Simon R, Songhorabodi S *et al.* Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of patterns of recurrence. *Surgery* 1986; **100**: 278–84.
9. Iwatsuki S, Esquivel CO, Gordon RD, Starzl TE. Liver resection for metastatic colorectal cancer. *Surgery* 1986; **100**: 804–10.
10. Lise M, Da Pian PP, Nitti D, Pilati PL, Prevaldi C. Colorectal metastases to the liver: present status and management. *Dis Colon Rectum* 1990; **33**: 688–94.
11. Nordlinger B, Quilichini MA, Parc R, Hannoun L, Delva E, Huguet C. Hepatic resection for colorectal liver metastases – influence on survival of preoperative factors and surgery for recurrences in 80 patients. *Ann Surg* 1987; **205**: 256–63.
12. Sesto ME, Vogt DP, Hermann RE. Hepatic resection in 128 patients: a 24-year experience. *Surgery* 1987; **102**: 846–51.
13. Scheele J, Stangl R, Altendorf-Hofmann A, Gall FP. Indicators of prognosis after hepatic resection for colorectal secondaries. *Surgery* 1991; **110**: 13–29.
14. Fujimoto S, Miyasaki M, Higuchi M, Okui K. Long term survivors of colorectal cancer with unresectable hepatic metastases. *Dis Colon Rectum* 1984; **28**: 588–91.
15. Registry of hepatic metastases. Resection of the liver for colorectal carcinoma metastases: a multi-institutional study of indications for resection. *Surgery* 1988; **103**: 278–88.
16. Scheele J, Stangl R, Altendorf-Hofmann A. Hepatic metastases from colorectal carcinoma: impact of surgical resection on the natural history. *Br J Surg* 1990; **77**: 1241–6.
17. Adson MA. Resection of liver metastases – when is it worthwhile? *World J Surg* 1987; **11**: 511–20.
18. August DA, Sugarbaker PH, Ottow RT, Gianola FJ, Schneider PD. Hepatic resection of colorectal metastases – influence of clinical factors and adjuvant intraperitoneal 5-fluorouracil via Tenckhoff catheter on survival. *Ann Surg* 1985; **201**: 210–18.
19. Bozzetti F, Bignami P, Morabito A, Doci R, Gennari L. Patterns of failure following surgical resection of colorectal cancer liver metastases – rationale for a multimodal approach. *Ann Surg* 1987; **205**: 264–70.
20. Ekberg H, Tranberg KG, Andersson R *et al.* Patterns of recurrence in liver resection for colorectal secondaries. *World J Surg* 1987; **11**: 541–7.
21. Fortner JG. Recurrence of colorectal cancer after hepatic resection. *Am J Surg* 1988; **155**: 378–82.
22. Wagner JS, Adson MA, Van Heerden JA, Adson MH, Ilstrup DM. The natural history of hepatic metastases from colorectal cancer – a comparison with resective treatment. *Ann Surg* 1984; **199**: 502–8.
23. Bozzetti F, Bignami P, Montalto F, Doci R, Gennari L. Repeated hepatic resection for recurrent metastases from colorectal cancer. *Br J Surg* 1992; **79**: 146–8.
24. Bradpiece HA, Benjamin IS, Halevy A, Blumgart LH. Major hepatic resection for colorectal liver metastases. *Br J Surg* 1987; **74**: 324–6.
25. Gennari L, Doci R, Bozzetti F, Bignami P. Surgical treatment of hepatic metastases from colorectal cancer. *Ann Surg* 1986; **203**: 49–54.
26. Couinaud C. *Le Foie. Etudes Anatomiques et Chirurgicales.* Paris: Masson, 1957: 283–468.
27. Dagradi AD, Mangiante GL, Marchiori LA, Nicoli NM. Repeated hepatic resection. *Int Surg* 1987; **72**: 87–92.
28. Stone MD, Cady B, Jenkins RL, McDermott WV, Steele GD. Surgical therapy for recurrent liver metastases from colorectal cancer. *Arch Surg* 1990; **125**: 718–22.
29. Vogt P, Raab R, Ringe B, Pichlmayr R. Resection of synchronous liver metastases from colorectal cancer. *World J Surg* 1991; **15**: 62–7.
30. Morrow CE, Grage TB, Sutherland DER, Najarian JS. Hepatic resection for secondary neoplasms. *Surgery* 1982; **92**: 610–14.
31. Petrelli NJ, Nambisan RN, Herrera L, Mittelman A. Hepatic resection for isolated metastasis from colorectal carcinoma. *Am J Surg* 1985; **149**: 205–9.
32. Cady B, Stone MD. The role of surgical resection of liver metastases in colorectal carcinoma. *Semin Oncol* 1991; **18**: 399–406.
33. Lange JF, Leese T, Bismuth H. Repeat hepatectomy for recurrent malignant tumors of the liver. *Surg Gynecol Obstet* 1989; **169**: 119–26.
34. Gouillat C, Partensky C, Duque Campos R, Bérard P. Les résections hépatiques itératives après hépatectomie réglée pour métastases des cancers digestifs. *Lyon Chirurgical* 1991; **87**: 376–8.
35. Clarke MP, Kane RA, Steele G *et al.* Prospective comparison of preoperative imaging and intraoperative ultrasonography in the detection of liver tumors. *Surgery* 1989; **106**: 849–55.

36. Delva E, Camus Y, Nordlinger B *et al.* Vascular occlusions for liver resections. *Ann Surg* 1989; **209**: 211–18.
37. Huguet C, Nordlinger B, Galopin JJ, Bloch P, Gallot D. Normothermic hepatic vascular exclusion for extensive hepatectomies. *Surg Gynecol Obstet* 1978; **147**: 689–93.
38. Huguet C, Bona S, Nordlinger B, Lagrange L, Harb J, Benard F. Repeat hepatic resection for primary and metastatic carcinoma of the liver. *Surg Gynecol Obstet* 1990; **171**: 398–402.
39. Griffith KD, Sugarbaker PH, Chang AE. Repeat hepatic resections for colorectal metastases. *Surgery* 1990; **107**: 101–14.
40. Joyeux H, Saint-Aubert B, Szawlowski AW, Astre C, Solassol C. Chirurgie carcinologique pour des métastases hépatiques diffuses. *Chirurgie* 1987; **113**: 113–16.
41. Nakamura S, Yokoi Y, Suzuki S, Baba S, Muro H. Results of extensive surgery for liver metastases in colorectal carcinoma. *Br J Surg* 1992; **79**: 35–8.
42. Tomas de la Vega JE, Donahue EJ, Doolas A *et al.* A ten year experience with hepatic resection. *Surg Gynecol Obstet* 1984; **159**: 223–8.
43. Attiyeh FF, Wichern WA. Hepatic resection for primary and metastatic tumors. *Am J Surg* 1988; **156**: 368–73.
44. Brown DA, Pommier RF, Woltering EA, Fletcher WS. Nonanatomic hepatic resection for secondary hepatic tumors with special reference to hemostatic technique. *Arch Surg* 1988; **123**: 1063–6.
45. Minton JP, Hamilton WB, Sardi A, Nieroda C, Sickle-Santanello B, O'Dwyer PJ. Results of surgical excision of one to 13 hepatic metastases in 98 consecutive patients. *Arch Surg* 1989; **124**: 46–8.
46. O'Grady JG, Polson RJ, Rolles K, Calne RY, Williams R. Liver transplantation for malignant disease – results in 93 consecutive patients. *Ann Surg* 1988; **207**: 373–9.

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Announcement

Surgery of the Liver, Biliary System and Pancreas

The British Council are holding a course devoted to Surgery of the Liver, Biliary System and Pancreas in The Royal College of Surgeons of Edinburgh from 17 to 23 October 1993. The course is intended for discussion of complex issues with an audience composed of relatively senior specialist surgeons. Topics to be covered will include: cholelithiasis and choledocholithiasis; minimally invasive hepatobiliary surgery; transplantation of liver and pancreas; acute and chronic pancreatitis; pancreatic and periampullary cancer; hepatobiliary trauma; portal hypertension; and hepatic and biliary malignancy. The course will be directed by Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh.

Further information can be obtained from: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK.

D. C. Carter

Short note

Br. J. Surg. 1993, Vol. 80, March, 345

Ultrasonography in the diagnosis of gallbladder polyps

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Polyps of the gallbladder are rare lesions, which can be defined as tumours or tumour-like projections arising from the mucosa of the organ. The true incidence of gallbladder polyps is unknown. In published data, around 80 per cent of such lesions are found in women, and they occur most commonly in the fourth decade of life[1]. The most frequent symptoms are dyspepsia, cramping abdominal pain, epigastric and right upper quadrant discomfort, and other symptoms resembling the clinical features of chronic gallbladder disease. Diagnosis is most commonly made by ultrasonography; however, the usefulness of this technique in identifying such polyps is controversial. The present prospective study was therefore designed to determine the reliability of ultrasonography in the diagnosis of gallbladder polyps.

Patients and methods

Between 1983 and 1991, 23 patients were diagnosed by ultrasonography as having gallbladder polyps. Diagnosis was made on the basis of single or multiple fixed echoes that projected into the lumen of the gallbladder and which had no acoustic shadow. All of these patients underwent cholecystectomy; the operative specimens were examined histopathologically and results correlated with the preoperative ultrasonographic appearances.

Results

There were 17 women and six men; the age range was 23–72 (mean 43) years. Gallbladder polyps were found in only 13 patients by histopathological examination (*Table 1*).

In the ultrasonographic study the diameter of the non-shadowing echogenic foci measured 2–3 mm in five patients, 4–5 mm in ten and 6–7 mm in eight.

Table 1 *Results of histopathological examination in 23 patients*

	No. of patients
Gallbladder polyps	13
Chronic calculous cholecystitis	6
Chronic acalculous cholecystitis	3
Normal gallbladder	1

The interval between the ultrasonographic study and cholecystectomy ranged from 2 to 30 (mean 7·2) days. Two patients whose first ultrasonographic studies were performed in other centres were examined for a second time in this department; both were found to have gallbladder polyps on histopathological examination.

Discussion

Diagnosis of gallbladder polyps is relatively easy and is readily made with ultrasonography. This method has advantages over other imaging techniques because of its ability to demonstrate very small lesions. The non-shadowing single or multiple fixed echoes that project into the lumen of the gallbladder and are detected by ultrasonography are regarded as gallbladder polyps[2,3]. Other lesions that may mimic polyps include small gallstones impacted in the wall, thick bile (sludge ball) or mucosal folds[3]. However, it becomes harder to determine the exact nature of the lesion as the diameter of the mass projecting into the gallbladder lumen decreases.

In the present study six patients were found to have gallstones. The diameter of four of these lesions was $\leqslant 5$ mm. In four patients no lesion was found in the gallbladder.

In summary, the results of this study reveal that ultrasonographic criteria for the diagnosis of gallbladder polyps need to be revised and repeated ultrasonographic studies should be performed at intervals, especially for small lesions, to improve diagnostic accuracy.

References

1. Arbab AA, Brasfield R. Benign tumors of the gallbladder. *Surgery* 1967; **61**: 535–40.
2. Berk RN, van der Vegt JH, Lichtenstein JE. The hyperplastic cholecystoses: cholesterolosis and adenomyomatosis. *Radiology* 1983; **146**: 593–601.
3. Weill FS. Rare abnormalities of the bile ducts, congenital anomalies, and tumors. In: Weill FS, ed. *Ultrasound Diagnosis of Digestive Diseases*. Heidelberg: Springer-Verlag, 1990: 349–66.

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Short note

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Impact of laparoscopic cholecystectomy in the UK: a survey of consultants

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The rapid adoption of laparoscopic cholecystectomy has raised questions about training and practice. The extent to which this technique has become established in surgical practice in the UK, how surgeons are trained for the procedure and the source of funding used to introduce it were investigated.

Results

A questionnaire was sent to 1031 consultant general surgeons working in the UK; identifying information was removed from all replies. A total of 783 surgeons replied (75·9 per cent); of these, 691 (88·3 per cent) performed cholecystectomy. Laparoscopic cholecystectomy was being performed by 386 surgeons and 212 planned to introduce it. Only 103 of those performing cholecystectomy (14·9 per cent) did not intend to undertake the laparoscopic procedure and cited the following reasons: too old or about to retire (45 respondents); operation performed by colleagues (22); mainly subspecialized (20); no advantage or deemed to be dangerous (12); too busy (two); not interested (one); and other reasons (one).

The number of laparoscopic cholecystectomies performed by the 386 surgeons and the rates of conversion to an open procedure are shown in *Table 1*.

Of the 457 surgeons who responded to the question about funding, 260 (56·9 per cent) had been funded through conventional National Health Service resources. The remainder were financed from waiting list initiatives, trust funds or charitable donations.

Of the 618 surgeons responding to questions of training, only ten (1·6 per cent) felt that specific training for laparoscopic cholecystectomy was unnecessary yet 113 (18·3 per cent) had taught themselves without attending formal courses. Some 491 (79·4 per cent) had studied videos of the technique and 320 (51·8 per cent) had visited another surgeon to observe or assist at laparoscopic cholecystectomy; 411 (66·5 per cent) had invited surgeons experienced in the operation to assist in their own hospital. Only 54 (8·7 per cent) had trained on an animal model while 196 (31·7 per cent) had attended training courses offering hands-on experience.

Of surgeons already performing laparoscopic cholecystectomy, 53 (13·7 per cent) would have preferred more training before introducing the procedure, as did 67 (31·6 per cent) of those still planning to introduce it. In the preceding 5 years 252 surgeons (36·5 per cent) had routinely performed diagnostic laparoscopy.

All surgeons who had performed more than 50 procedures had converted to open operation at least once but there was a trend to lower conversion rates with increasing experience (*Table 1*). Of 197 surgeons who were not performing laparoscopic cholecystectomy, 113 operated a policy of routine cholangiography while 55 were selective. Of the surgeons performing laparoscopic cholecystectomy, 54 undertook routine cholangiography, 121 performed cholangiography selectively and 193 not at all.

Table 1 *Laparoscopic cholecystectomies performed and percentages converted to open procedures*

No. of operations performed by each surgeon	No. of surgeons	No. of surgeons who have never converted to open operation	Median (range) rate of conversion to open operation (%)
1–10	207	128	0 (0–100)
11–20	71	22	8 (0–27)
21–30	47	5	7 (0–20)
31–40	16	2	4 (0–12)
41–50	18	2	4 (0–31)
51–60	8	0	5 (2–9)
61–100	4	0	4 (2–5)
>100	15	0	3 (1–11)

Several surgeons thought that the difficulties of learning the procedure and the requirements for training had been overemphasized. Only five remained unconvinced of the advantages of laparoscopic cholecystectomy. A recurring complaint was of lack of National Health Service funding to start the service.

Discussion

By the end of 1991 the majority of general surgeons in the UK undertaking cholecystectomy had started or intended to start performing laparoscopic cholecystectomy. Only 15 of the present respondents (1·9 per cent) were not convinced of its advantages. It is difficult to know whether surgeons in the UK have embarked on this procedure without adequate training because reports of deaths resulting from the procedure and of common bile duct injury are largely anecdotal, as are reports of significant morbidity. The present study has shown that the majority of surgeons favour formal training including workshops and hands-on courses; these skills will be relevant as other laparoscopic techniques are introduced.

It is likely that, compared with nearly 40 per cent in this survey, all general surgeons (excepting those in subspecialties) will become regular and experienced laparoscopists. Similarly, all surgical training programmes will inevitably have to include laparoscopic training. The lessons learned from the introduction of laparoscopic cholecystectomy should be applied to other minimally invasive techniques with regard to guidelines and training. Laparoscopic cholecystectomy has, in a remarkably short time, become firmly established in surgical practice in the UK.

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Fully implantable venous access systems

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Central access systems are a considerable step forward in the treatment of patients with cancer. Experience with totally implantable vascular access systems is reported. Since 1986, 185 reservoir pumps have been implanted. Access was by percutaneous cannulation of the subclavian vein in 130 cases (70 per cent) and surgical exposure of the external jugular vein in 40 (22 per cent); other sites of insertion were used in 15 cases (8 per cent). The mean duration of use of the reservoirs was 276 (range 1–632) days (total 51 150 catheter-days). The mean number of injections was 390 (range 2–670). The total number of complications, mostly mechanical, was 25 (0·5 per 1000 catheter-days). Fully implantable venous access systems are safe and reliable, and their complications can be prevented with adequate management.

Venous access for chemotherapy in patients with cancer has been considered to represent a physical risk as well as a psychological problem. Antineoplastic drugs are often severely irritating, leading to destruction of available surface vessels.

The Silastic (Dow Corning, Reading, UK) right atrial catheters described by Broviac *et al.*[1] and Hickman and colleagues[2] represented a great step to achieve safer and less painful vascular access. The high rates of sepsis and thrombosis associated with these catheters have nevertheless limited their use[3,4]. To decrease these complications, fully implantable vascular access systems were devised[5,6].

The present study analyses the results obtained in this department from the use of totally implantable venous access systems in patients with malignant disease.

Patients and methods

Since 1986, 185 implantable catheter systems have been placed in 176 patients of whom 108 (61·4 per cent) were women (*Table 1*). The mean age of the patients was 53 (range 16–79) years.

Two types of reservoir were used. The Port-a-Cath (Pharmacia, Milton Keynes, UK) system was initially placed by inserting the catheter through the dissected cephalic vein in the deltopectoral groove. This technique was applied in no more than 15 cases (8·1 per cent); it was substituted by surgical exposure of the external jugular vein because the cephalic vein was often of small calibre or obliterated. The improved procedure of placement of this type of reservoir was used in 40 cases (21·6 per cent). The Implantofix (B. Braun, Melsungen, Germany) was placed by percutaneous cannulation of the subclavian vein, using a technique developed in this department. A 1-cm incision is made in the infraclavicular fossa, using local anaesthesia and sterile technique. Through the incision, the subclavian vein is punctured by the usual procedure; however, this is done using a split cannula (Splittocan; B. Braun) with an internal lumen of 1·9 mm which allows introduction of the Implantofix catheter (external diameter 1·7 mm). Then the cannula is divided, and the skin incision enlarged to 3 cm to develop the subcutaneous pocket. The port is placed into the pouch and sutured to the pectoral fascia. The entire procedure requires 5–10 ml local anaesthetic agent and the mean duration of placement was 15 min. This method was used in 130 cases (70·3 per cent).

Results

The total number of catheter-days was 51 150 for a mean catheter working time of 276 (range 1–632) days. The mean number of injections was 390 (range 2–670).

A total of 29 patients died with a working device in place. There were 25 complications (0·5 per 1000 catheter-days of treatment), the most frequent of which were mechanical (*Table 2*). Extravasation occurred in seven cases (3·8 per cent) and venous thrombosis in five (2·7 per cent). Only four patients (2·3 per cent) developed catheter-related sepsis, giving an incidence of sepsis of less than one episode each year and a rate of infection of 1 per 12 788 patient-days. In 18 cases the reservoirs had to be removed because of the complications. The implantable pump was replaced by another in nine patients.

Table 1 *Diagnosis of malignant tumours in 176 patients*

Diagnosis	No. of patients
Colorectal cancer	47 (26·7)
Breast cancer	37 (21·0)
Pharyngeal cancer	21 (11·9)
Sarcoma	15 (8·5)
Oesophagogastric cancer	10 (5·7)
Lung cancer	7 (4·0)
Endometrial cancer	6 (3·4)
Liver cancer	5 (2·8)
Lymphoma	5 (2·8)
Other	23 (13·1)

Values in parentheses are percentages

Table 2 *Complications occurring in 25 cases*

Complication	No. of cases
Mechanical (occlusion)	
Anomalous position	1
Catheter bent	2
Thrombosis	5
Extravasation	7
Venous thrombosis	5
Sepsis	4
Alterations in electrocardiogram	1

Discussion

Vascular access for patients who require long-term drug delivery was a serious and challenging problem until the development of fully implantable venous access systems. These devices have enabled complete mobility and a more normal life for patients with neoplastic disease. Recently, controlled studies have shown that these reservoirs are safer and better tolerated than traditional external catheters[7] and allow a significantly longer infection-free duration of use[8]. Since 1986 the number of devices implanted in this department has been increasing. It is worth noting that, in the past 2 years, no complications led to the removal of the reservoir.

Among the possible complications, extravasation was caused by improper needle placement in all cases. This problem previously always required the withdrawal of the reservoir.

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Now, with greater experience and well trained nurses, this complication has become much less frequent.

Venous thrombosis was not related to the duration of the treatment. A major alteration of the coagulation system was found in four patients and the fifth needed multiple punctures to cannulate the subclavian vein.

The incidence of catheter thrombosis was practically the same with the two systems despite the fact that these had a different internal lumen. This result is not in agreement with previous reports[9,10] and no explanation has been suggested.

When there was clinical evidence of general infection, the device was removed only after an exhaustive investigation of other possible causes of sepsis. The four catheter infections encountered in the present patients were confirmed by culture of the same organism (*Staphylococcus epidermidis* in three cases, *Escherichia coli* in one) from both the catheter tip and blood. The rate of infection in the present series (1 per 12 788 patient-days) is much lower than that reported with percutaneous catheters (1 per 465 patient-days)[11].

The correct selection of insertion site is of utmost importance. The 6-year experience of this department indicates that the preferred site of insertion is the subclavian vein by means of a direct venous puncture. This is a rapid, secure and easy procedure. The subcutaneous pocket is created beside the venous puncture and does not require a subcutaneous tunnel. When it is impossible to cannulate the subclavian vein, direct dissection of the external jugular vein is carried out.

In summary, totally implantable venous access systems are reliable and safe, and provoke a minimal tissue reaction. Placement must be by a trained operator, and both nurses and patients have to be adequately trained to optimize the benefits of the devices and reduce complications as much as possible.

References

1. Broviac JW, Cole JJ, Scribner BH. A silicone rubber atrial catheter for prolonged parenteral alimentation. *Surg Gynecol Obstet* 1973; **136**: 602–6.
2. Hickman RO, Buckner CD, Clift RA, Sanders JE, Stewart P, Thomas ED. A modified right atrial catheter for access to the venous system in marrow transplant recipients. *Surg Gynecol Obstet* 1979; **148**: 871–5.
3. Bothe A, Piccione W, Ambrosino JJ *et al.* Implantable central venous access system. *Am J Surg* 1984; **147**: 565–9.
4. Thomas JH, MacArthur RI, Pierce GP *et al.* Hickman–Broviac catheters. *Am J Surg* 1980; **140**: 791–5.
5. Peters JL, Belsham PA, Taylor BA, Watt-Smith S. Long-term venous access. *Br J Hosp Med* 1984; **13**: 230–42.
6. Champault G. Catheters totalement implantables pour chimiotherapie anticancéreuse. *J Chir (Paris)* 1985; **122**: 269–72.
7. Carde P, Cosset-Delaigue MF, Laplanche A, Chareau I. Classical external indwelling central venous catheter *versus* totally implanted venous access systems for chemotherapy administration: a randomized trial in 100 patients with solid tumors. *Eur J Cancer Clin Oncol* 1989; **25**: 939–44.
8. Mirro J Jr, Rao BN, Stokes DC *et al.* A prospective study of Hickman/Broviac catheters and implantable ports in pediatric oncology patients. *J Clin Oncol* 1989; **7**: 214–22.
9. August L. Totally implantable indwelling catheter system. Alternative techniques of insertion. *Angiology* 1985; **36**: 715–19.
10. Niederhuber J, Ensminger W, Gyves J, Liepman M, Doan K, Cozzi E. Totally implanted venous and arterial access system to replace external catheters in cancer treatment. *Surgery* 1982; **92**: 706–12.
11. Pessa ME, Howard RJ. Complications of Hickman–Broviac catheters. *Surg Gynecol Obstet* 1985; **161**: 257–60.

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Lipomatous polyposis of the colon

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Although lipomas are the third most common benign colonic tumours after adenomatous and hyperplastic polyps, they are uncommon neoplasms[1]. Usually submucosal in position and single, they are sometimes multiple but still few in number[2]. Diffuse lipomatous polyposis of the colon is a very rare condition. A patient with colonic lipomatous polyposis that was thought to represent a carcinoma complicating familial adenomatous polyposis is presented.

Case report

A 58-year-old man presented with a 1-year history of intermittent abdominal pain frequently associated with bloody diarrhoea. In the past 2 months the patient had lost 4 kg in weight. Examination revealed no abnormality. The abdomen was soft and non-tender with normal peristalsis. On colonoscopy, more than 50 small smooth polypoid lesions were seen from 28 cm above the anus to the mid-transverse colon. At this point there was a firm ulcerated infarcted mass with the appearance of an adenocarcinoma. It was obstructing the colonic lumen, so the ascending colon was not examined. Biopsy only showed vascular granulation tissue.

At laparotomy, examination of the large intestine revealed numerous intraluminal polypoid tumours and a rounded mass in the middle of the transverse colon. A radical resection of the transverse colon was performed.

Histological examination showed a segment of colon containing 47 submucosal sessile and occasionally pedunculated lipomas of sizes varying from 2 mm to 5 cm in diameter (*Figure 1a*). The largest polyps filled the colonic lumen and were markedly haemorrhagic and ulcerated (*Figure 1b*). Microscopic examination revealed the lipomatous nature and submucosal position of the polyps. A few of the largest lipomas were not only submucosal but subserosal in location, having a dumb-bell appearance (*Figure 2*).

Recovery was uneventful and the patient was discharged 12 days after operation.

Discussion

Intestinal lipomas are usually single, asymptomatic and located in the right colon[1–3]. Most reports of multiple lipomas of the large bowel describe a small number of polyps: two or three but rarely more than four[1,2]. Diffuse lipomatous polyposis of the colon is an exceptional condition[4].

Although most lipomas are incidental findings, they occasionally precipitate a surgical emergency such as intussusception, obstruction or bleeding[1–5]. Multiple polyp-

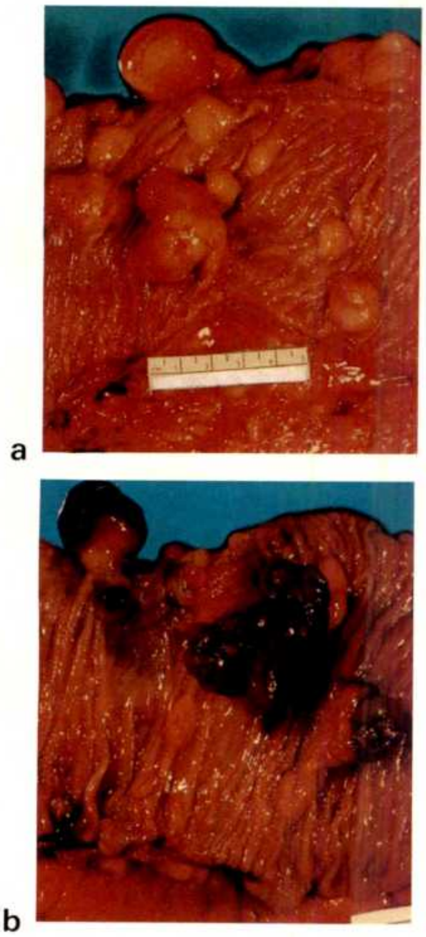

Figure 1 *Resected specimens:* **a** *segment of colon showing multiple sessile pedunculated lipomas;* **b** *partially ulcerated and necrotic appearance of lipomas mimicking a malignant tumour*

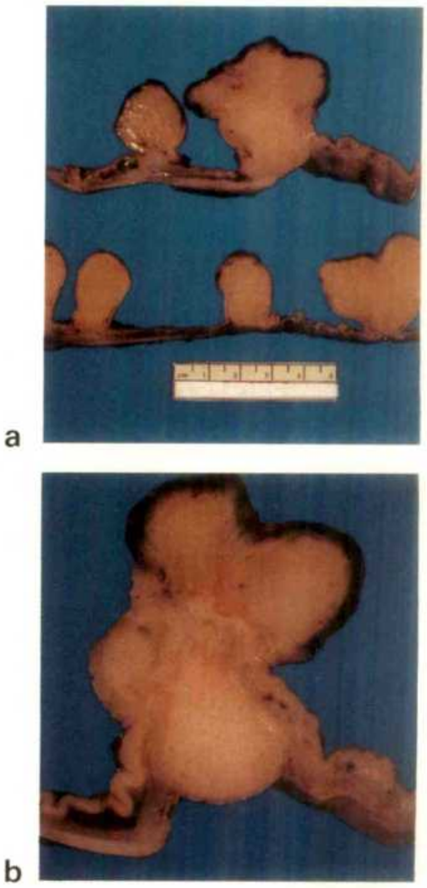

Figure 2 **a** *Segment of colon showing submucosal and subserosal location of lipomas.* **b** *Dumb-bell lipoma*

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ectomies, performed endoscopically or through serial enterotomies, may be considered for scanty lipomas, but local excision conserving as much colon as possible or segmental excision of the area of intestine that contains the greatest concentration of lipomas may be necessary in cases such as the one reported here[4].

It is worth noting the ability of intestinal lipomas to simulate premalignant and malignant conditions, posing a significant problem in diagnosis and treatment[5]. Surgeons have occasionally resorted to extensive resection because of the difficulty of excluding malignancy on gross appraisal. Lipomas must always be considered in the differential diagnosis of intra-abdominal neoplasms, particularly in the investigation of intestinal obstruction and obscure haemorrhage.

References

1. Taylor BA, Wolff BG. Colonic lipomas. Report of two unusual cases and review of the Mayo Clinic experience, 1976–1985. *Dis Colon Rectum* 1987; **30**: 888–94.
2. Ling CS, Leagus C, Stahlgren LH. Intestinal lipomatosis. *Surgery* 1959; **46**: 1054–9.
3. Ryan J, Martin JE, Pollock DJ. Fatty tumours of the large intestine: a clinicopathological review of 13 cases. *Br J Surg* 1989; **76**: 793–6.
4. Castro B, Stearns MW. Lipoma of the large intestine: a review of 45 cases. *Dis Colon Rectum* 1972; **15**: 441–4.
5. Mayo CW, Pagtalunan RJG, Brown DJ. Lipoma of the alimentary tract. *Surgery* 1963; **53**: 598–603.

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Photoplethysmography in the diagnosis of superficial venous valvular incompetence

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Photoplethysmography was compared with clinical investigation combined with Doppler ultrasonography in the diagnosis of superficial venous valvular incompetence of the lower limb. In 268 consecutive patients, 536 limbs were investigated. A total of 22·1 per cent of the photoplethysmographic investigations were uninterpretable because they did not allow reliable determination of the refilling time. Agreement between clinical investigation combined with Doppler ultrasonography and photoplethysmography was found to be poor ($\kappa = 0{\cdot}30$). These results suggest that photoplethysmography is not the non-invasive method of choice for routine evaluation of superficial venous valvular incompetence of the leg.

Since the report by Abramowitz *et al.*[1] in 1979, in which photoplethysmography was compared with venous pressure measurements in the diagnosis of deep venous valvular incompetence, photoplethysmography has been described in various publications as a quantitative, reliable, rapid, reproducible and non-invasive method of testing the venous system[1–5]. Consequently, this technique has found widespread use in the diagnosis of venous disorders of the leg. However, various authors have questioned the criteria for interpretation of the results of photoplethysmography as well as its reproducibility[6–11].

In contrast to the allegedly quantitative photoplethysmography, Doppler ultrasonography is a qualitative method. It provides information on the presence of venous valvular incompetence with a high degree of sensitivity and specificity[12–15]. Recently, quantitative aspects of venous (duplex) Doppler ultrasonographic studies have also been published[16]. In modern clinical practice Doppler ultrasonography is among the techniques most used to complement clinical examination in the diagnosis of superficial venous valvular incompetence[13].

A study was undertaken to compare the value of photoplethysmography with that of the combination of clinical examination and Doppler ultrasonography in the diagnosis of superficial venous valvular incompetence of the lower limb.

Patients and methods

The study included 268 consecutive patients (201 women, 67 men) consulting the surgical department for the first time for varicosities of the lower limbs. The mean age was 44 (range 17–76) years. A total of 536 limbs were examined with photoplethysmography, clinical investigation and Doppler ultrasonography. A control group of five healthy men and six healthy women (total 22 limbs) without clinical manifestation of venous insufficiency underwent the same examinations. The mean age of the controls was 32 (range 25–50) years. Photoplethysmography was performed twice in the controls to study the reproducibility of the measurement.

Photoplethysmography

A photoplethysmograph consists of a transducer, an amplifier and a recorder. The transducer emits infra-red light into the underlying tissues. The backscattered light is received by a photodetector and the resulting signal displayed on a stripchart recorder. The shift from the baseline reflects the degree of filling of the cutaneous capillarovenous plexus; it reflects the combination of arterial inflow, venous outflow and venous reflux in the limb[2]. The transducer (EC4 plethysmograph; Hewlett–Packard, Andover, Massachusetts, USA) was fixed to the skin near the medial malleolus, taking care not to place it directly over the long saphenous vein (LSV). Recordings were obtained with the patient sitting with feet in a non-weight-bearing position. When a stable baseline was obtained at rest, the patient was instructed to perform dorsiflexion of the foot at the rate of one movement per second. During dorsiflexion the subcutaneous plexus is emptied, which deflects the photoplethysmographic signal from the baseline. Ideally this deflection will return to the original baseline after cessation of exercise. The time needed for this return is known as the venous refilling time. A time >20 s is generally considered normal and one ≤20 s abnormal and indicative of venous reflux[2]. By repeating the test with a tourniquet or cuff with a pressure greater than the local venous pressure applied above the knee, below the knee and at calf level, further differentiation of the nature of the valvular incompetence is possible[12]. In this study sphygmomanometer cuffs were used. Limbs with deep venous insufficiency had refilling times (with cuffs) ≤15 s, whereas those with superficial venous valvular incompetence had times (with cuffs) >15 s and ≤20 s.

Four different outcomes of photoplethysmography may be obtained:

1. Normal result while testing without the cuff, indicative of a haemodynamically normal venous system without valvular incompetence.
2. Abnormal result that normalizes after placement of a high thigh cuff occluding the LSV, indicative of isolated valvular incompetence of the LSV.
3. Abnormal result that does not normalize after placement of a high thigh cuff occluding the LSV, considered to be an indication of a more complex venous valvular incompetence, such as valvular incompetence of the short saphenous vein (SSV), deep venous valvular incompetence, valvular incompetence of perforator veins,

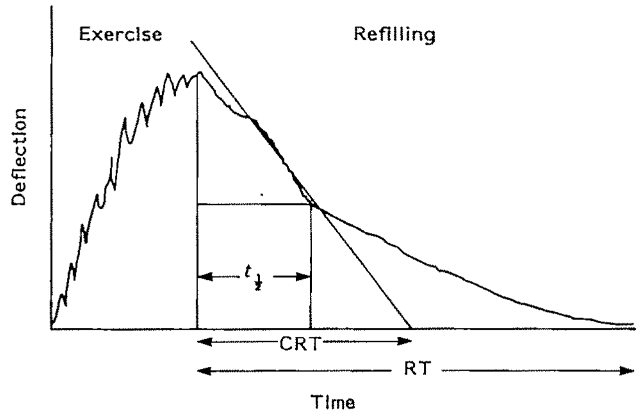

Figure 1 *Schematic representation of a photoplethysmographic recording with venous refilling time (RT), venous half-refilling time ($t_{1/2}$) and calculated venous refilling time (CRT) indicated*

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or combinations of these with or without LSV valvular incompetence.

4. A non-interpretable recording obtained with or without the cuff, making categorization in one of the above three groups impossible.

Non-interpretable photoplethysmographic curves consisted of two types: either the deflection from the baseline did not return to the baseline position after cessation of muscle activity, or the curves showed continued drifting away from the baseline after exercise. In an attempt to reduce the problem of non-interpretability, two other parameters from the recordings were used (*Figure 1*). First, the venous half-refilling time ($t_{1/2}$), defined as the time necessary for the baseline shift to return to 50 per cent of its maximal deflection from baseline, was calculated. Normal values[2] for $t_{1/2}$ are reported as >9 s. Second, the tangent of the first part of the recovery slope was drawn and the calculated venous refilling time taken as the time from the point of maximum deflection to the intercept of this tangent with the original baseline. The reported[4] normal value for this time is >20 s.

Clinical investigation

All clinical investigations were performed by two vascular surgeons and consisted of inspection, palpation of varicosities and tourniquet tests. Tourniquet testing was aimed at finding LSV valvular incompetence by observing varicose veins being prevented from filling by a high thigh tourniquet and filling retrogradely on release of the tourniquet. In a similar way, saphenopopliteal and perforator vein valvular incompetence was sought with below-knee tourniquets. Based on these examinations all legs were classified according to presence or absence of LSV valvular incompetence.

Doppler ultrasonography

The Doppler ultrasonography velocity detector permits qualitative assessment of valvular incompetence in the deep, communicating and superficial veins of the lower limb. By placing the Doppler transducer directly on the vein and using distal compression, physiological flow can be observed. During proximal compression, reflux can be heard if there is valvular incompetence. Occasionally a short refluxing signal (<1 s) may be heard, which is not regarded as pathological. The Doppler ultrasonographic investigations for this study were performed using a bidirectional continuous-wave device (Vascular Doppler Medasonics, Mountain View, California, USA). The resulting signals were judged acoustically by two experienced vascular laboratory technicians. The patient lay supine during femoral vein and posterior tibial vein examination. The popliteal vein was tested with the patient in a prone position. The standing position was used for examination of the LSV at the saphenofemoral junction, for the LSV at below-knee level, and for the SSV. Reflux at the saphenofemoral junction was tested by the Valsalva manoeuvre.

Classification

The results of clinical investigation were combined with those of ultrasonography to reach a final classification of the limbs for comparison with the photoplethysmographic classification. Limbs were classified as normal, as having isolated valvular incompetence of the LSV, or as having a complex pattern of incompetence (valvular incompetence of the SSV, perforating veins, deep veins or combinations of the three).

Statistical analysis

The mean values for the three measures of refilling time were compared by Student's t test; agreement between clinical–ultrasonographic and photoplethysmographic classification was expressed as a kappa (κ) value[17,18]. This measurement of agreement has values in the range 0–1 (0 meaning no agreement at all and 1 complete agreement). A clinically relevant test should have $\kappa \geqslant 0{\cdot}6$.

Results

Table 1 compares clinical–ultrasonographic and photoplethysmographic classification. The total number of non-interpretable photoplethysmographic tests was 118 (22·1 per cent of the total). The final classification divided them into 53 with no venous valvular incompetence, 54 with isolated LSV valvular incompetence and 11 with complex valvular incompetence. The non-interpretable photoplethysmographic tests were equally distributed over the three classifications. The agreement between clinical–ultrasonographic and photoplethysmographic classification was very poor. Excluding the non-interpretable photoplethysmographic results, the κ value (as a measure of agreement) was 0·30. Including the non-interpretable results, the κ value was 0·21. *Table 2* gives the various measures of refilling time for limbs with and without venous valvular incompetence and for those of healthy controls. For controls the mean of two measurements was taken. The mean refilling

Table 2 *Mean(s.d.) values for parameters of venous refilling in limbs with and without venous valvular incompetence and normal controls*

	Venous refilling time (s)	Venous half-refilling time (s)	Calculated venous refilling time (s)
Incompetence	22(13)	17(13)	31(20)
No incompetence	17(11)	11(11)	25(21)
Controls	31(21)		

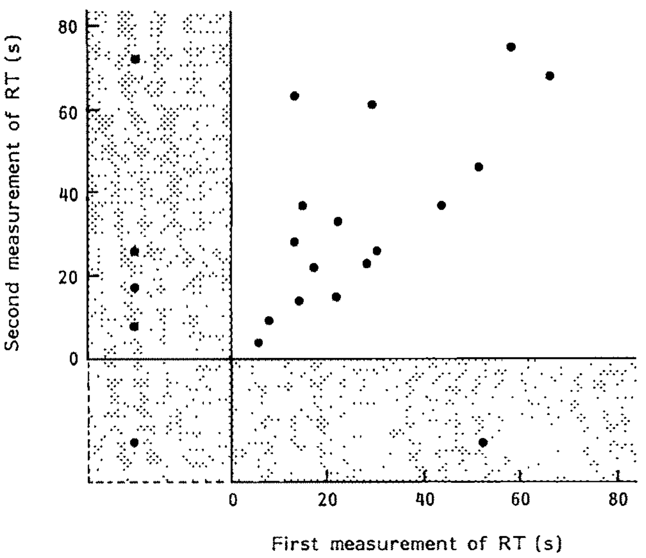

Figure 2 *Comparison between two measurements of refilling time (RT) in healthy control limbs. Measurements shown in the shaded area were not interpretable*

Table 1 *Comparison between clinical–ultrasonographic and photoplethysmographic classification*

	Photoplethysmographic classification				
Clinical–ultrasonographic classification	Normal	LSV incompetence	Complex	Non-interpretable	Total
Normal	118	22	39	53	232
LSV incompetence	57	52	38	54	201
Complex	20	14	55	11	100
Total	195	88	132	118	533*

LSV incompetence, isolated long saphenous vein valvular incompetence; complex, valvular incompetence of short saphenous vein, perforating veins, deep veins or combinations of the three. *Technical problems occurred in testing three of the 536 limbs time, half-refilling time and calculated refilling time for the legs with and without any form of venous valvular incompetence was significantly different ($P < 0.001$), but the standard deviation was so large that this difference has no clinical relevance for the individual patient. The number of non-interpretable photoplethysmographic curves was high: 95 for refilling time, 269 for half-refilling time and 124 for calculated refilling time.

Figure 2 shows the correlation between the first and second measurements in healthy controls. In controls the mean(s.d.) refilling time was 29(19) s for the first measurement and 34(23) s for the second. The numbers of non-interpretable measurements in the controls were five and two respectively.

Discussion

The introduction of photoplethysmography by Barnes in 1973 and the observations by Abramowitz *et al.* in which the technique provided information comparable to that obtained by venous pressure studies in deep venous insufficiency[1] greatly encouraged the use of this method. Although first described in the diagnosis of the postphlebitic syndrome, there was later growing interest in its application for the detection of superficial venous valvular incompetence[3,4,6,7]. The technique provided the clinician with a simple non-invasive method of studying venous haemodynamics and of documenting the effect of therapy. Invasive pressure measurements have been replaced by non-invasive methods such as photoplethysmography over the past 10 years. Attempts to duplicate the favourable initial results proved disappointing: in healthy limbs, refilling times were found within the abnormal range, and minor exercise and clinical conditions associated with reactive hyperaemia resulted in shortening of the refilling time below the criterion for normality[3]. Measurements such as the half and calculated venous refilling times were introduced to make photoplethysmography more accurate. Their reliability varies according to different authors[1,3,4,6,8]. Many explanations have been given for the variety of photoplethysmographic results. The technique picks up a strong skin reflection that disturbs the recordings substantially[10,14]. All photoplethysmography devices are sensitive to the illumination of the surroundings; a lighted lamp within 1 m from the transducer can give a change in signal of a magnitude similar to that of the signal itself[5]. The pressure with which the transducer is fixed to the skin is important, because different pressures give substantially different recordings[14]. Furthermore, photoplethysmographic recordings are dependent on skin[3] and room[11] temperature, skin pigmentation and haematocrit[3,11,19–21]. Although the precise location of the sensor was not found to be critical, placement directly over the saphenous vein or a varix should be avoided[6]. Recently published work suggests that photoplethysmographic refilling times reflect regional haemodynamics rather than overall venous haemodynamics in the limb[22].

Review of the original articles reporting favourable results with the technique reveals that these were obtained by repeated studies on the same limb. Divergent values were thus readily identified and, by excluding them from the calculation or by averaging the refilling times for a given limb and thereby diminishing the effect of a single divergent value, favourable results were obtained. The number of repeated measurements varied from three to five. In the present study, comparing photoplethysmography with clinical investigation combined with Doppler ultrasonography gave disappointing results. The refilling time was found to have a poor correlation with clinical investigation and ultrasonography. The number of non-interpretable photoplethysmographic recordings was found to be unacceptably high. Non-interpretable photoplethysmographic recordings had an equal distribution over the subgroups of venous valvular incompetence and do not in themselves have diagnostic meaning. Other approaches, such as the half and calculated venous refilling times, gave no better discrimination and led to an even higher proportion of non-interpretable recordings. In conclusion, the present study suggests that photoplethysmography is not the non-invasive method of choice in the routine evaluation of superficial venous valvular incompetence.

References

1. Abramowitz HB, Queral LA, Flinn RW *et al.* The use of photoplethysmography in the assessment of venous insufficiency: a comparison to venous pressure measurements. *Surgery* 1979; **86**: 434–41.
2. Barnes RW, Yao JST. Photoplethysmography in chronic venous insufficiency. In: Bernstein EF, ed. *Non-invasive Diagnostic Techniques in Vascular Disease.* St Louis, Missouri: Mosby, 1982: 514–34.
3. Norris CS, Beyrau A, Barnes RW. Quantitative photoplethysmography in chronic venous insufficiency: a new method of non-invasive estimation of ambulatory venous pressure. *Surgery* 1983; **94**: 759–63.
4. Kempczinski RF, Berlatzky Y, Pearce WH. Semi-quantitative photoplethysmography in the diagnosis of lower extremity venous insufficiency. *J Cardiovasc Surg (Torino)* 1986; **27**: 17–23.
5. Fisher M, Wuppermans T. Vergleich der Wertigkeit der Phlebodynamometrie mittels unbluttiger Infrarot Photoplethysmographie und bluttiger Druckmessung. *Phlebologie und Proctologie* 1982; **11**: 259–63.
6. Burnham SJ. Varicose veins: patient selection and treatment. In: Rutherford RB, ed. *Vascular Surgery.* Philadelphia, Pennsylvania: WB Saunders, 1989: 1513–17.
7. Barnes RW, Ross EA, Strandness DE. Differentiation of primary from secondary varicose veins by Doppler ultrasound and strain gauge plethysmography. *Surg Gynecol Obstet* 1975; **141**: 207–11.
8. Barnes RW. Doppler techniques for evaluation of lower extremity venous disease. In: Bergan JJ, Yao JST, eds. *Surgery of the Veins.* Orlando, Florida: Grune and Stratton, 1984: 99–109.
9. Pearce WH, Rico JP, Queral LA, Flinn WR, Yao JST. Hemodynamic assessment of venous problems. *Surgery* 1983; **93**: 715–19.
10. Weindorf N, Schulz-Ehrenburg U. Der Wert der Photoplethysmographie in der Phlebologie. *Vasa* 1986; **15**: 397–403.
11. Eikirson E. Photoplethysmographic studies of venous disease of the legs. *Acta Chir Scand Suppl* 1986; **540**: 398–401.
12. Colgan MP, Sumner DS. How does a vascular laboratory influence the management of venous disease? In: Greenhalgh RM, Jamieson CW, Nicolaides AN, eds. *Vascular Surgery. Issues in Current Practice.* London: Grune and Stratton, 1986: 119–31.
13. Schraibman IG. The diagnosis of saphenofemoral incompetence. In: Negus D, Jantet G, eds. *Phlebology 1985.* London: J Libbey, 1986: 92–3.
14. Wienert V. Funktionelle Phlebologische Diagnostik mit Hilfe der Licht-Reflexions-Rheographie. *Dtsch Med Wochenschr* 1984; **25**: 997–9.
15. McIrvine AJ, Corbett CRR, Aston NO, Sherriff EA, Wiseman PA, Jamieson CW. The demonstration of saphenofemoral incompetence. Doppler ultrasound compared with standard clinical tests. *Br J Surg* 1984; **71**: 509–10.
16. Bemmelen PS, Bedford G, Beach K, Strandness DE. Quantitative segmental evaluation of venous valvular reflux with duplex ultrasound scanning. *J Vasc Surg* 1989; **10**: 425–31.
17. Schouten HJA. Measuring pairwise agreement among many observers. *Biomedical Journal* 1980; **22**: 497–504.
18. Koran LM. Reliability of clinical methods, data and judgements. *N Engl J Med* 1975; **293**: 642–6, 695–701.
19. Ris HB, Gfeller CH, Mahler F, Nachbur B. Comparative evaluation of three ambulatory plethysmographic devices as regards accuracy and handling in daily practice. *Eur J Vasc Surg* 1991; **5**: 159–64.
20. Raju S, Fredericks R. Evaluation of methods for detecting venous reflux: perspectives in venous insufficiency. *Arch Surg* 1990; **125**: 1463–7.
21. Van den Broek ThAA. *Chronic venous insufficiency and venous reconstructive surgery.* PhD Thesis, Vrije University, Amsterdam, 1989.
22. Rosfors S. Venous plethysmography, relationship between transducer position and regional distribution of venous insufficiency. *J Vasc Surg* 1990; **11**: 436–40.

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Cardiac risk and peripheral vascular surgery: new approach based on a multifactorial risk index

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An inexpensive approach to stratification of patients admitted for arterial surgery into groups of high and low cardiac risk has been prospectively evaluated in 235 consecutive patients. The Goldman and Detsky indices, assessed by a nurse the day before surgery, both identified patient groups with increased risk of lethal or potentially lethal (myocardial infarction, pulmonary oedema) cardiac events within 30 days after peripheral vascular surgery. The Goldman index was the more sensitive predictor of cardiac death (overall frequency 3·1 per cent) while the Detsky index was superior for prediction of non-lethal cardiac events (overall frequency 5·9 per cent). The simplest and yet most effective stratification into high and low cardiac risk was achieved using a Detsky score of 10 as the cut-off. It is concluded that multifactorial risk index-based preoperative screening can identify low-risk patients (Detsky score $\leqslant 10$), who may be accepted for vascular surgery (aortic aneurysm surgery excluded) without additional cardiac testing.

Patients undergoing peripheral arterial procedures are known to be at increased risk, compared with general surgical patients, because of generalized atherosclerotic involvement predisposing to a high incidence of cardiac complications in the perioperative period[1,2]. Preoperative identification of high-risk patients is important both for a proper assessment of the risk–benefit ratio for surgery and to allow more intense perioperative management of those at high risk to reduce complication rates[3–5]. Cost containment should benefit from preoperative identification of low-risk patients using simple, inexpensive and yet effective techniques; the resources needed for more complicated and expensive tests of cardiac function could then be reserved for a smaller group of patients at greater risk.

The multifactorial indices of cardiac risk in non-cardiac surgery introduced by Goldman *et al.*[6,7] and modified by Detsky and colleagues[8,9] have been shown to allow stratification of patients into several different risk categories. However, the multifactorial risk assessment in these studies has been carried out by general physicians, cardiologists and/or anaesthetists and is consequently associated with significant cost. Since relatively simple and straightforward clinical data are mainly evaluated, it may be argued that such screening by a highly specialized doctor is unnecessary. This prospective study was therefore carried out to test the hypothesis that preoperative assessment by a nurse, using the Goldman[6,7] and Detsky[8,9] multifactorial cardiac risk indices, is effective for primary stratification of patients into groups at low and high cardiac risk. All patients studied were considered suitable candidates for arterial surgery by a senior vascular surgeon.

Patients and methods

Patients

Patients were seen first by one of three senior vascular surgeons at the outpatient clinic. Non-operative treatment was chosen when the risk–benefit ratio for surgery was considered unacceptable. All other patients were admitted for arterial surgery, in some cases following consultation with a cardiologist or general physician, and were included in the study. During a 27-month period, 235 patients of mean(s.d.) age 70(11) years undergoing 256 arterial surgical procedures were included. The 235 were consecutive except that no patients were included when the nurse was not on duty (approximately 9 weeks each year). A total of 218 patients underwent one vascular procedure and 17 more than one. One of two senior vascular surgeons performed 85 per cent of procedures. All patients gave informed consent. Emergency cases (surgery performed within 24 h after emergency admission) with acute lower-limb ischaemia who were operated on during office hours were included whenever possible, i.e. when the nurse had the opportunity to assess the patient before emergency operation. Baseline clinical characteristics and operative risk factors are shown in *Table 1*.

Surgery

The operations performed are shown in *Table 2*. Endarterectomy and patch angioplasty were used for stenosis of vascular graft anastomoses or of the deep femoral artery. Expanded polytetrafluoroethylene (PTFE) prostheses were used for extra-anatomic bypass and woven Dacron (Du Pont, Wilmington, Delaware, USA) grafts were employed for aortic surgery. Fogarty catheter thromboembolectomy for arterial thromboembolism was performed semielectively, whenever possible. The indications for elective operation on patients with lower-limb ischaemia were critical ischaemia in 85 per cent and incapacitating intermittent claudication in 15 per cent. Femorodistal arterial bypass was performed using the saphenous vein *in situ* as an arterial conduit, except for bypass to the popliteal artery above the knee (PTFE). The mean(s.d.) preoperative ankle arterial systolic pressure in patients undergoing elective operation for lower-limb ischaemia was 37(28) mmHg.

Anaesthesia and postoperative management. Patients undergoing femorofemoral bypass or surgery below the inguinal ligament were operated on under continuous epidural or spinal anaesthesia; axillofemoral, aortic and carotid procedures were performed under general anaesthesia. Thromboembolectomy was carried out under spinal, epidural or local anaesthesia. Preoperative evaluation not

Table 1 *Patient details*

	No. of patients ($n = 235$)
Sex ratio (M:F)	149:86 (63·4–36·6)
Previous or current smokers	181 (77·0)
Complicating conditions	
Diabetes	46 (19·6)
Arterial hypertension	107 (45·5)
Chronic renal failure	12 (5·1)
Severe bronchopulmonary disease	29 (12·3)
Previous myocardial infarction	98 (41·7)
Previous stroke	40 (17·0)

Values in parentheses are percentages

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pertaining to the study protocol was performed according to standard clinical routines: chest radiography, electrocardiogram (ECG), baseline laboratory tests and evaluation by the anaesthetist. A general physician or cardiologist was consulted before operation whenever this was considered necessary by the vascular surgeon or anaesthetist.

During operation and for the first 12–24 h after surgery, ECG and oxygen saturation (pulse oximetry) were continuously monitored. Patients who underwent aortic surgery were usually ventilated artificially during the first 12–24 h after operation. Heparin (5000 units twice daily subcutaneously) was used for prophylaxis of thromboembolism.

Table 2 *Operations performed and frequency of potentially lethal complication and cardiac death*

Procedure	No.	Potentially lethal cardiac complication*	Cardiac death	Total (%)†
Endarterectomy or patch angioplasty	28 (10·9)	3	1	14
Thromboembolectomy	25 (9·8)	1	4	20
Femoropopliteal bypass	35 (13·7)	1	0	3
Femorocrural or pedal bypass	22 (8·6)	3	1	18
Aortoiliac or aorto-femoral bypass	18 (7·0)	1	0	6
Aneurysm resection below inguinal ligament	11 (4·3)	1	0	9
Exploration (bypass not possible)	13 (5·1)	1	2	23
Extra-anatomic bypass	29 (11·3)	1	0	3
Abdominal aortic aneurysm repair	29 (11·3)	2	0	7
Carotid endarterectomy	40 (15·6)	1	0	2
Other arterial surgery	6 (2·3)	0	0	0
Total	256 (100)			

Values in parentheses are percentages. *Acute myocardial infarction, pulmonary oedema or life-threatening arrhythmia; †potentially lethal cardiac complication or cardiac death

Study protocol

Preoperative assessment. All patients were interviewed and examined by the same registered nurse throughout the study on the day of admission, for practical reasons. The nurse had had 15 years of experience as a nurse anaesthetist and before the start of the study underwent 1 week of training in evaluation of the risk factors included in the Goldman and Detsky cardiac risk indices (*Table 3*). Recording of angina pectoris according to the Canadian Cardiovascular Society[10], previous myocardial infarction or pulmonary oedema was based on the interview and previous medical records, whereas rhythm disturbances on admission were identified on the preoperative ECG which, routinely, was analysed by a cardiologist. A physical examination of the heart was made by the nurse. In the case of a cardiac murmur not described in previous medical records a cardiologist was consulted. Poor general medical condition was recorded mainly according to the criteria described by Goldman *et al.*[6,7], but often using oxygen saturation measured by a pulse oximeter rather than blood gas analyses of partial pressures of oxygen and carbon dioxide. The data collected by the nurse were unavailable to the physicians involved in the treatment of the patient.

Assessment of postoperative cardiac events. The day before surgery, serum aspartate aminotransferase and creatine phosphokinase (CPK) levels were determined. ECGs were taken on the first, second and seventh days after operation and enzymes were routinely analysed on days 1 and 2. When myocardial infarction was suspected, blood samples were repeated; creatinine phosphokinase isoenzymes (CPK-MB) were analysed whenever CPK levels were increased. A cardiologist was consulted when there was a clinical suspicion of an intraoperative or postoperative cardiac event. Potentially lethal cardiac complications in the interval between discharge from hospital up to day 30 after operation were registered at the follow-up check that occurred between 30 and 60 days after surgery. At the end of the study the medical records of all patients in whom an intraoperative or postoperative cardiac event could not be excluded were reviewed for classification by an independent cardiologist who was unaware of the data collected by the nurse. All deaths within 6 months of surgery were recorded.

Definition of endpoints. An acute myocardial infarction, which was one of the primary endpoints, was considered diagnosed when at least two of the following three criteria were met: (1) an episode of chest pain, discomfort, substernal pressure or heaviness lasting >30 min; (2) a transient peak in total CPK concentration reaching at least twice the normal level and with a CPK-MB subfraction >5 per cent of total

Table 3 *Goldman and Detsky cardiac risk indices and the frequency of risk factors for 256 arterial procedures*

Risk factor	Score: Goldman	Score: Detsky	No. of cases ($n = 256$)	Potentially lethal cardiac complication or cardiac death (%)
Myocardial infarction				
Within 6 months	10	10	11 (4·3)	36*
>6 months ago	—	5	87 (34·0)	12
Canadian Cardiovascular Society angina score				
Class III	—	10	27 (10·5)	19
Class IV	—	20	6 (2·3)	33†
Unstable angina within ≤3 months	—	10	8 (3·1)	13
Preoperative electrocardiogram rhythm other than sinus	7	5	37 (14·5)	16
>5 premature ventricular contractions per min ever documented	7	5	22 (8·6)	14
Suspected severe aortic valvular disease	3	20	3 (1·2)	0
S3 gallop or jugular vein distension	11	—	35 (13·7)	17
Age >70 years	5	5	142 (55·5)	11
Emergency operation	4	10	17 (6·6)	29*
Intraperitoneal, intrathoracic or aortic operation	3	—	48 (18·8)	6
Poor general medical status‡	3	5	49 (19·1)	22*
Pulmonary oedema				
Within 1 week	—	10	8 (3·1)	63*
Ever	—	5	41 (16·0)	17†
Maximal score possible	53	100		

Values in parentheses are percentages. *$P < 0·01$; †$P < 0·05$ (*versus* patients without risk factor, Fisher's exact test); ‡according to criteria of Goldman *et al.*[6,7]

CPK; and (3) Minnesota code criteria for definite or probable myocardial infarction accompanied by evolving ST and T wave changes[11]. Since the first criterion cannot be met during general anaesthesia, a new Q wave observed in a postoperative ECG was also taken as evidence of acute infarction, even when the enzyme criterion was not met (for instance, CPK and CPK-MB levels increased but CPK-MB remaining <5 per cent of total CPK). When there was an inconclusive rise in enzyme level and no new Q wave (i.e. a transmural myocardial infarction was ruled out, but a subendocardial infarction was not) a diagnosis of possible subendocardial infarction was made. Severe congestive heart failure was diagnosed if the patient had typical clinical and chest radiographic findings. Lethal and potentially lethal cardiac complications were recorded separately. A cardiac death was diagnosed if a patient died from either arrhythmia or progessive low cardiac output not explained by a non-cardiac disease. Potentially lethal cardiac complications were defined as non-lethal definite acute infarction (possible subendocardial infarction excluded), pulmonary oedema or life-threatening arrhythmia (ventricular tachycardia lasting >1 min or haemodynamically compromising the patient, ventricular fibrillation, or complete atrioventricular block) during the first month after operation. Other cardiac events in the postoperative period were not considered potentially lethal and were disregarded in the analysis. Autopsy was performed in fatal cases.

Data analysis

The relationship between cardiac risk indices and cardiac events was analysed by logistic regression. The Goldman and Detsky index scores were used as independent variables and cardiac death, potentially lethal cardiac complications, possible subendocardial infarction and all deaths within 6 months of surgery as dependent variables. Using χ^2 analysis, risk classes, consisting of ranges of Goldman and Detsky index scores giving a maximal F ratio (i.e. optimal risk stratification), were identified. The differences in risk between these classes were analysed using Fisher's exact test.

Results

The overall cardiac complication rates according to the different definitions are shown in *Table 4*. Ten patients (3·9 per cent) died within 30 days. There were two non-cardiac deaths (one from malignant disease, one from cerebral infarction) and eight cardiac deaths, giving an overall cardiac mortality rate of 3·1 per cent (1·3 per cent for elective surgery). Potentially lethal cardiac complications were non-lethal acute infarction (13 cases) and postoperative pulmonary oedema without verified acute myocardial infarction (two). A total of 15 potentially lethal cardiac complications were thus observed, representing 5·9 per cent of procedures (*Table 4*). The overall rate of cardiac death and potentially lethal complications was 9·0 per cent. Possible subendocardial infarction was diagnosed in another 23 patients (9·0 per cent). The overall survival rate at 6 months was 87·6 per cent.

Early follow-up was complete in all cases and follow-up of deaths within 6 months complete in all but nine. Data on two cardiac risk variables were missing and the Goldman and Detsky index scores were therefore not calculated for two patients. There were no cardiac complications in these two cases. Two patients did not appear at the 30-day follow-up; neither of these was readmitted or died within 30 days after surgery, but the possibility of a potentially lethal cardiac complication cannot be completely ruled out.

Approximately 60 per cent of all patients undergoing emergency surgery for acute lower-limb ischaemia during the study period were included. No patient considered operable by a senior vascular surgeon, and thus included in the study and evaluated by the nurse, was cancelled from surgery. Most patients had Goldman and Detsky index scores <10; mean(s.d.) scores were 8(8) and 11(11) respectively. Regarding different indications for surgery, patients with acute limb ischaemia had the highest mean(s.d.) score: Goldman index 15(11) and Detsky 21(14). The risk indices were significantly related ($P < 0·001$ for both scores) to the incidence of postoperative cardiac complications. The Detsky score was more closely related to non-lethal acute myocardial infarction whereas the Goldman score was a better predictor of cardiac death (*Table 4*). The risk of potentially lethal cardiac complication and cardiac death increased with increasing Detsky index score for all types of vascular surgery other than abdominal aortic aneurysm (AAA) repair. For aneurysm repair there were two non-lethal acute infarctions, both of which were observed in patients with Detsky index scores ⩽5.

The original Goldman index classes[7] did not discriminate optimally when applied to the present series. The ranges of scores that most significantly discriminated cardiac risk in χ^2 analysis, for the Goldman as well as Detsky index *versus* the primary endpoints, were identified (*Table 4*). For both indices, maximum discrimination was achieved using three risk classes. With the Detsky index, a low-risk group of 128 cases (50·0 per cent) without cardiac deaths and with a 2·3 per cent incidence of potentially lethal complications was identified. For cardiac death, the Goldman index identified a low-risk class of 197 cases (77·0 per cent) with a cardiac death rate of 1·0 per cent. The proportion of lethal cardiac events in the combined total of potentially lethal complication and cardiac deaths increased with increasing risk scores. Death within 6 months of surgery was significantly more common in patients with a perioperative potentially lethal complication than in those without (31 *versus*

Table 4 *Cardiac complication rates*

	Potentially lethal cardiac complication*	Possible subendocardial myocardial infarction†	Cardiac death	Potentially lethal cardiac complication or cardiac death	Cardiac death (%)‡	Death within 6 months of follow-up
Overall (%)	5·9 ($n = 15$)	9·0 ($n = 23$)	3·1 ($n = 8$)	9·0 ($n = 23$)	35	12·4 (28 of 226)**
Goldman cardiac risk index score						
⩽12 ($n = 197$)	5·6(1·7)	8·2(2·0)	1·0(0·7)	6·6(1·8)	18	7·1(2·0)
13–26 ($n = 50$)	8(4·1)	14(5·3)	6(3·4)	14(5·0)	43	23(6·1)
>26 ($n = 7$)	0	50(29)	43(20·2)	43(20·2)	100	57(20·2)
P§	n.s.	0·013	0·0001†	0·002	—	0·0001¶
Detsky cardiac risk index score						
⩽5 ($n = 128$)	2·3(1·3)	8·0(2·4)	0	2·3(1·3)	0	4·8(2·1)
6–20 ($n = 92$)	8(2·9)	10(3·3)	3(1·9)	11(3·3)	30	17(4·1)
>20 ($n = 34$)	18(7·1)	21(8·5)	15(6·2)	29(7·9)	50	21(7·2)
P§	0·007	n.s.	0·0001	0·0001¶	—	0·006

Values in risk index score classes are mean(s.d.) percentages. *Excluding cardiac death; †excluding potentially lethal cardiac complications and cardiac death; ‡proportion of potentially lethal cardiac complications plus cardiac death; §overall P for χ^2 analysis (i.e. P for overall discrimination by the ranges of risk scores indicated); ¶complication rates in all three risk classes in the χ^2 analysis are significantly different ($P < 0·05$) by Fisher's exact test; **nine of the 235 patients were not followed up for 6 months; n.s., not significant

Table 5 *Optimal stratification of patients undergoing peripheral vascular surgery into high and low cardiac risk groups*

	Detsky score ≤ 10*				Detsky score >10†			
	No.	Potentially lethal cardiac complication or cardiac death	Cardiac death	Death within 6 months of follow-up	No.	Potentially lethal cardiac complication or cardiac death	Cardiac death	Death within 6 months of follow-up
All cases (excluding abdominal aortic aneurysm)	151	2·0(1·1)	0	4·0(1·8)	74	24(5·0)	11(3·6)	28(5·4)
Cases of abdominal aortic aneurysm	22	9(6·3)	0	9(6·3)	7	0	0	0

Values are mean(s.d.) percentages. *Low cardiac risk; †high cardiac risk

8·8 per cent, $P < 0{\cdot}01$). No such difference was observed between patients with and without a possible subendocardial infarction.

The final stratification into one low- and one high-risk group of peripheral vascular surgical patients was then made (*Table 5*). Optimal stratification was achieved using Detsky index scores of ≤ 10 and >10: survival at 6 months was significantly different in these two groups. Since the Detsky index score proved to be less valid for AAA repair, patients with aneurysm are presented separately (*Table 5*).

Discussion

Preoperative assessment of the risk of lethal or potentially lethal perioperative cardiac events is important because this has therapeutic implications. Surgery can be postponed or cancelled in high-risk cases and preoperative institution of risk-reducing treatment may be employed. For practical reasons, the assessment in this study was performed the day before surgery. In clinical practice it may be preferable for the nurse to evaluate the patient in the clinic at the first visit to the surgeon.

Many different approaches for risk assessment in patients undergoing vascular surgery have been suggested. These include risk equations based on general cardiovascular factors[1], analyses of automated physiological profile systems[12], ambulatory preoperative ECG monitoring[13] and other invasive or non-invasive measurements[14,15]. The present study shows that preoperative calculation of the Detsky risk index[8,9] by a nurse is an effective and inexpensive method for primary stratification of vascular surgical patients into high- and low-risk groups.

The high frequency of cardiac complications in the present study is considered to be caused by increased perioperative stress in patients with severe atherosclerotic disease. Patients with peripheral atherosclerotic disease have a shorter life expectancy than the general age-matched population; in those with severe limb ischaemia a monthly mortality rate of 0·8–1·2 per cent has been reported[16].

Both the Goldman and Detsky risk indices were evaluated. Three classes with significantly different risks of potentially lethal (Detsky index) and lethal (Goldman index) cardiac complications were first identified. Using the Goldman index classes, a large low-risk group, containing 77·0 per cent of the patients, with a 1-month mortality rate similar to that expected even without an operation and with <6 per cent incidence of potentially lethal cardiac complications, was identified. Using the corresponding Detsky index classes, a low-risk group (50·0 per cent of patients) with no cardiac deaths and a 2·3 per cent rate of potentially lethal cardiac complications was demonstrated. Extreme high-risk groups could also be identified. However, the objective of identifying one high-risk and one low-risk group was best accomplished using the Detsky index.

The present method for risk stratification was found to be less useful for the 29 patients undergoing AAA repair. This observation is in agreement with previous reports[17,18] and seems to be because aortic surgery, owing to its complexity, imposes a higher cardiac risk than predicted by criteria developed from a broad base of surgical patients. For other types of vascular surgery, optimal stratification into low- and high-risk groups was obtained using a Detsky index score of 10 as the cut-off. No patient with a Detsky index score ≤ 10 died within 30 days and only 2·0 per cent (patients with aortic aneurysm excluded) suffered a potentially lethal cardiac complication. The sensitivity of low-risk group stratification was 98·0 per cent (148 of 151 cases correctly classified).

The present study defines cardiac death, definite acute myocardial infarction, pulmonary oedema and life-threatening arrhythmia within 1-month of surgery as primary endpoints. The definition of the first endpoint leaves little room for discussion; that of the others, however, is less exact, and so lethal and potentially lethal cardiac complications have been presented separately. Coding of acute myocardial infarction, as defined in the International Classification of Diseases (ICD-9-CM)[19], is already a problem in the coronary care unit because of clinical uncertainties at admission and interpretation difficulties in the ECG and enzyme findings[20]. The certainty of a perioperative acute myocardial infarction has additional problems; anaesthesia and sedation may mask or alter the symptoms of an infarction. Furthermore, levels of several enzymes may increase as a result of muscle injury and/or ischaemia in association with arterial surgery[21]. Therefore, the symptom criterion is often not met, whereas an inconclusive enzyme release is frequently observed. A significant group of patients in whom the diagnosis of a minor infarction is uncertain seems, therefore, unavoidable in studies of perioperative cardiac complications. In this study 13 patents either had new Q waves or met at least two of the three defined infarction criteria, and the diagnosis of acute myocardial infarction accordingly seemed certain. In another 23 cases, however, a minor acute infarction could be neither excluded nor confirmed. The prognostic importance of such a possible minor infarction is limited, however, as the prognosis after a myocardial infarction is to a large extent related to the amount of myocardium lost[22]. In accordance with this, survival at 6 months in patients with and without a possible subendocardial infarction did not differ in the present series. This group has been reported separately and conclusions based on the observed incidence of definite lethal or potentially lethal cardiac complications.

Preoperative invasive or non-invasive cardiodynamic tests measuring left ventricular ejection fraction and cardiac output in different situations may be used to predict perioperative cardiac complications[23–26]. Continuous ECG recordings may detect silent myocardial ischaemic attacks and so possibly identify patients at high risk[27,28]. Myocardial thallium scintigraphy with or without stress tests may reveal poorly vascularized myocardium and be used for risk evaluation[29,30]. These techniques are time consuming, expensive and may be associated with complications. They may, however, be necessary for risk screening in patients scheduled for AAA repair. The presently described simple and inexpensive technique for risk stratification proved to be highly effective for patients with all other types of peripheral vascular disease. In previous studies[6–9], the preoperative evaluation was performed by experienced doctors. The data collected in the present study by the nurse were clinically useful. It is suggested that patients admitted for arterial surgery (excluding AAA repair) are evaluated using this approach. Those at low risk may be accepted for surgery without further evaluation, whereas more extensive tests or consultations may be selectively applied to the smaller group at high risk, thereby reducing overall cost while retaining a high level of safety for the patient.

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References

1. Cooperman M, Pflug B, Martin EW Jr, Evans WE. Cardiovascular risk factors in patients with peripheral vascular disease. *Surgery* 1978; **84**: 505–9.
2. Hertzer NR, Beven EG, Young JR *et al.* Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. *Ann Surg* 1984; **199**: 223–33.
3. Logue RB, Kaplan JA. The cardiac patient and noncardiac surgery. *Curr Probl Cardiol* 1982; **7**: 1–49.
4. Shah K, Kleinman B, Rao T *et al.* Reduction in mortality from cardiac causes in Goldman class IV patients. *Journal of Cardiothoracic Anesthesia* 1988; **2**: 789–91.
5. Rivers SP, Scher LA, Gupta SK, Veith FJ. Safety of peripheral vascular surgery after recent myocardial infarction. *J Vasc Surg* 1990; **11**: 70–6.
6. Goldman L, Caldera DL, Nussbaum SR *et al.* Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med* 1977; **16**: 845–50.
7. Goldman L, Caldera DL, Southwick FS *et al.* Cardiac risk factors and complications in non-cardiac surgery. *Medicine* 1978; **57**: 357–70.
8. Detsky AS, Abrams HB, Forbath N, Scott JG, Hilliard JR. Cardiac assessment for patients undergoing noncardiac surgery. A multifactorial clinical risk index. *Arch Intern Med* 1986; **146**: 2131–4.
9. Detsky AS, Abrams HB, McLaughlin JR *et al.* Predicting cardiac complications in patients undergoing non-cardiac surgery. *J Gen Intern Med* 1986; **1**: 211–19.
10. Campeau L. Grading of angina pectoris. *Circulation* 1976; **54**: 522–3.
11. Blackburn H, Keys A, Simonsen E *et al.* The electrocardiogram in population studies: a classification system. *Circulation* 1960; **21**: 1160–75.
12. Cohn JD, Engler PE, Del Guercio LRM. The automated physiologic profile. *Crit Care Med* 1975; **3**: 51–8.
13. Raby KE, Goldman L, Creager MA *et al.* Correlation between preoperative ischemia and major cardiac events after peripheral vascular surgery. *N Engl J Med* 1989; **321**: 1296–300.
14. Freeman WK, Gibbsons RJ, Shub C. Preoperative assessment of cardiac patients undergoing noncardiac surgical procedures. *Mayo Clin Proc* 1989; **64**: 1105–17.
15. Fleisher LA, Barash PG. Preoperative evaluation for non-cardiac surgery: a functional approach. *Anesth Analg* 1992; **74**: 586–98.
16. Jivegård L, Augustinsson LE, Carlsson CA, Holm J. Long-term results by epidural spinal electrical stimulation (ESES) in patients with inoperable severe limb ischemia. *Eur J Vasc Surg* 1987; **1**: 345–9.
17. Jeffrey CC, Kunsman J, Cullen DJ, Brewster DC. A prospective evaluation of cardiac risk index. *Anesthesiology* 1983; **58**: 462–4.
18. Lundqvist BW, Bergström R, Enghoff E *et al.* Cardiac risk in abdominal aortic surgery. *Acta Chirurgica Scandinavica* 1989; **155**: 321–8.
19. Public Health Service, US Department of Health and Human Services. *International Classification of Diseases, Ninth Revision, Clinical Modification.* Washington, District of Columbia: US Government Printing Office, 1970, Publication no. (RHS) 80-1260: 366–7.
20. Iezzoni LI, Burnside S, Sickles L, Moskowitz MA, Sawitz E, Levine PA. Coding of acute myocardial infarction. Clinical and policy implications. *Ann Intern Med* 1988; **109**: 745–75.
21. Möller-Petersen JM, Andersen PT, Lund L, Nielsen LK. Serum creatine kinase-B activity in patients with chronic lower-limb ischemia and after leg amputation. *Acta Chirurgica Scandinavica* 1989; **155**: 521–5.
22. Sanz G, Castaner A, Betriu A *et al.* Determinants of prognosis in survivors of myocardial infarction. *N Engl J Med* 1982; **306**: 1065–70.
23. Jivegård L, Arfvidsson B, Frid I, Haljamäe H, Holm J. Cardiac output in patients with acute lower limb ischemia of presumed embolic origin – a predictor of severity and outcome? *Eur J Vasc Surg* 1990; **4**: 401–7.
24. Babu SC, Sharma PVP, Raciti A *et al.* Monitor-guided responses. Operability with safety is increased in patients with peripheral vascular disease. *Arch Surg* 1980; **115**: 1384–6.
25. Berlauk JF, Abrams JH, Gilmour IJ, O'Connor SR, Knighton DR, Cerra FB. Preoperative optimization of cardiovascular hemodynamics improves outcome in peripheral vascular surgery. *Ann Surg* 1991; **214**: 289–97.
26. Loughlin V, Beniwal JS, Cassidy K, Russel C, Lalsingh R. Comparison of risk factor and left ventricular stroke work index as predictors of cardiac complications in vascular surgery. *Eur J Vasc Surg* 1990; **4**: 83–7.
27. Raby KE, Selwyn AP. Role of ambulatory ECG monitoring in estimating cardiac risk in vascular surgery patients. *Isr J Med Sci* 1989; **25**: 516–20.
28. McCann RL, Clements FM. Silent myocardial ischemia in patients undergoing periperal vascular surgery: incidence and association with perioperative cardiac morbidity and mortality. *J Vasc Surg* 1989; **9**: 583–7.
29. Stratmann HG, Mark AL, Walter KE, Williams GA. Preoperative evaluation of cardiac risk by means of atrial pacing and thallium-201 scintigraphy. *J Vasc Surg* 1989; **10**: 385–91.
30. McPhail NV, Ruddy TD, Calvin JE, Davies RA, Barber GG. A comparison of dipyridamole–thallium imaging and exercise testing in the prediction of postoperative cardiac complications in patients requiring arterial reconstruction. *J Vasc Surg* 1989; **10**: 51–6.

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Effect of seeding time and density on endothelial cell attachment to damaged vascular surfaces

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An in vitro *model to facilitate the study of endothelial cell seeding of damaged vascular surfaces has been developed. This may have applications in the study of endothelial seeding of angioplasty and endarterectomy sites. Using this model, the optimum endothelial seeding time for attachment to damaged vascular surfaces should not exceed 30 min and, to achieve confluent cell attachment, a seeding density* $>5 \times 10^5$ *cells/cm²* *should be used.*

Immediate endothelial cell seeding of prosthetic vascular grafts was initially described by Herring *et al.*[1] in 1978. Although studies in animal models have suggested that endothelial cell seeding may decrease platelet deposition, decrease thrombogenicity and increase patency rates[2-4] in prosthetic grafts, results from clinical trials have been largely disappointing[5-8]. Successful seeding of vascular prostheses in humans is hampered by poor initial endothelial cell harvest, low seeding efficiencies and poor cell retention on the luminal graft surface[9].

Endothelial cell seeding of damaged native vascular surfaces offers theoretical advantages over that of prosthetic materials. The area to be seeded will often be much smaller, reducing the number of endothelial cells required, and the subendothelial matrix exposed in damaged vessels should offer an excellent surface for endothelial cell attachment. Successful endothelial cell seeding of endarterectomy sites has previously been demonstrated in an animal model[10]. Endothelial cell seeding of percutaneous transluminal angioplasty (PTA) sites is an attractive proposition and has been achieved with moderate technical success by Nabel *et al.*[11] during their studies of gene transfer using endothelial cells. The present study describes development of an *in vitro* model that has been used to study the effects of seeding time and density on endothelial cell attachment to damaged vascular surfaces.

Materials and methods

Development of an in vitro *model of vascular damage*

Segments of previously undistended long saphenous vein, discarded during aortocoronary bypass grafting, were transported to the laboratory in chilled minimal essential medium (MEM; Flow Laboratories, High Wycombe, UK). The use of these was approved by the local ethical committee. The vein segments were immersed in MEM and threaded over a 5-mm balloon angioplasty catheter (Olbert catheter; Meadox, Dunstable, UK). The angioplasty balloon was inflated to 9 atm for 30 s, after which the vein was removed from the catheter. Vein segments were opened longitudinally, pinned on to a silicone gel plate and fixed under tension in 4 per cent paraformaldehyde–2 per cent glutaraldehyde solution.

Segments of vein were prepared for light and scanning electron microscopy. Segments for light microscopy were dehydrated through graded alcohol, transferred to xylene for 180 min and then immobilized in wax over a 4-h period. Serial sections of 4-μm thickness were subsequently stained with haematoxylin and eosin and elastic van Gieson stains.

Vein segments for electron microscopy were dehydrated through graded ethanol followed by acetone solutions before carbon dioxide critical-point drying and sputter-coating with gold. Sections were viewed on a DS130 scanning electron microscope (International Scientific Instruments, Buxton, UK).

Serial sections of dilated and non-dilated veins were independently reported by a pathologist (M.J.) unaware of the sample type.

Isolation and culture of endothelial cells

Endothelial cells were isolated from human umbilical vein by a method derived from Jaffe *et al.*[12]. Umbilical veins were cannulated at either end and filled with 5 ml 0·1 per cent collagenase solution (CLS I; Worthington Biochemical, Freehold, New Jersey, USA). After incubation for 15 min in a 95 per cent oxygen–5 per cent carbon dioxide atmosphere, the vein was flushed with 20 ml MEM and the resulting suspension centrifuged at 300*g* for 7 min at 4°C. The cell pellet was resuspended in 5 ml complete culture medium consisting of medium 199, 20 per cent fetal calf serum, 100 units/ml penicillin, 100 μg/ml streptomycin, 20 mmol/l *N*-2-hydroxyethylpiperazine-N′-2-ethanesulphonic acid buffer, 2 mmol/l glutamine, 1 mmol/l pyruvate, 15 μg/ml endothelial cell growth factor and 90 μg/ml heparin and plated on to a 25-cm² tissue culture flask. Cells were incubated at 37°C in a 95 per cent oxygen–5 per cent carbon dioxide atmosphere. Endothelial cell subculture was performed by brief trypsinization using 0·1 per cent trypsin in ethylenediamine tetra-acetic acid, centrifugation and resuspension in complete medium. Cells from the second and third subculture were used. Endothelial cell identity was confirmed by appearance at phase-contrast microscopy and positive immunohistochemical staining for von Willebrand factor (Dakopatts, Glostrup, Denmark).

Radiolabelling of endothelial cells

Human umbilical vein endothelial cells were labelled with indium-111 oxine by a method modified from Sharefkin *et al.*[13]. Cells were released from tissue culture by trypsinization, counted in a haemocytometer and centrifuged at 300*g* for 7 min. The cell pellet was resuspended in 0·5 ml MEM and incubated with 60 μCi indium-111 oxine (Amersham International, Amersham, UK) for 15 min. The cells were washed twice with MEM and finally resuspended in MEM with 5 per cent fetal calf serum at a known concentration. Labelling efficiency was determined at this time.

Attachment of endothelial cells to vein surface

The same methodology was used in experiments investigating both seeding time and seeding density. A 5-mm diameter punch biopsy of dilated saphenous vein was placed on silicone gel in a 5-mm diameter seeding chamber. A 100-μl aliquot of indium-111 labelled endothelial cell suspension, at a known concentration, was added to the seeding chamber so that the cells came into contact only with the luminal vein surface. After incubation in 95 per cent oxygen–5 per cent carbon dioxide for the allotted time, the unattached cells were removed by washing the luminal vein surface three times with MEM. The vein segment was removed and the seeding chamber washed twice further with MEM. All washings were collected. The radioactivity on the vein surface and in the washings (which contained the unattached cells) was measured. The percentage cell attachment was calculated using the formula:

$$\text{Per cent cell attachment} = \frac{\text{counts on vein}}{\text{counts on vein} + \text{counts in washings}} \times 100$$

Vein segments were fixed under tension after cell attachment had been determined, and prepared for light and electron microscopy as described previously.

Attachment of endothelial cells with time

In studying endothelial cell attachment with time, a cell seeding density of 1×10^5 cells/cm² was used in all experiments. This was a subconfluent seeding density, which ensured a maximal percentage cell

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attachment. Attachment of endothelial cells at 5, 10, 20, 30, 40 and 60 min was studied.

Attachment of endothelial cells with seeding density

A seeding time of 30 min was used in all experiments. Seeding densities from 1 × 10^4 to 1 × 10^7 cells/cm^2 were studied.

Results

Histological examination of dilated saphenous vein segments

Light microscopic examination of dilated saphenous vein segments revealed endothelial desquamation, rupture of the internal elastic lamina, longitudinal and circumferential tears in the tunica media, and stretching of the tunica media. Scanning electron microscopy confirmed complete endothelial desquamation over the dilated area with exposure of subendothelial connective tissue (*Figure 1*). Non-dilated vein segments showed patchy areas of endothelial cell loss but no damage to the deeper layers.

Endothelial cell attachment with time

The mean labelling efficiency in this set of experiments was 36 per cent (95 per cent confidence interval (c.i.) 31–40 per cent). The results for endothelial cell attachment have been expressed as percentage cell retention at given times (*Figure 2*). Cell attachment increased almost linearly with time up to 30 min, after which no further significant increase in cell retention occurred. The difference between mean cell attachment at 30 and 60 min was 2 per cent (99 per cent c.i. −14 to 10 per cent). Endothelial cell seeding was confirmed by both light and electron microscopy (*Figure 3*).

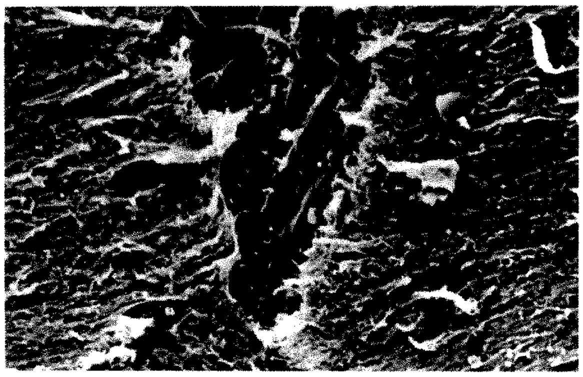

Figure 1 *Scanning electron micrograph of the luminal surface of a dilated saphenous vein segment. (Original magnification × 209)*

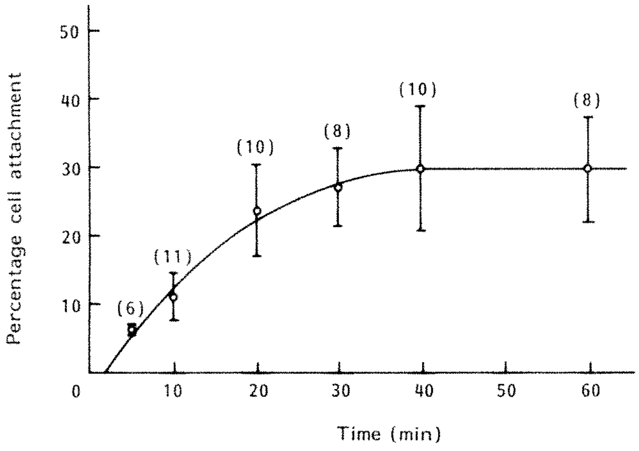

Figure 2 *Mean percentage cell retention at different seeding times. Bars are 95 per cent confidence intervals; values in parentheses are numbers of experiments*

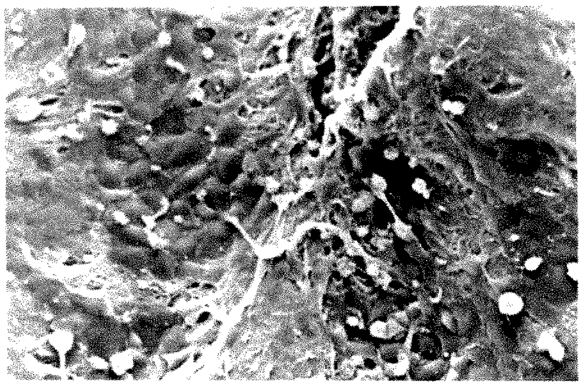

Figure 3 *Scanning electron micrograph showing endothelial cells attached to the luminal surface of a dilated seeded saphenous vein segment. (Original magnification × 249)*

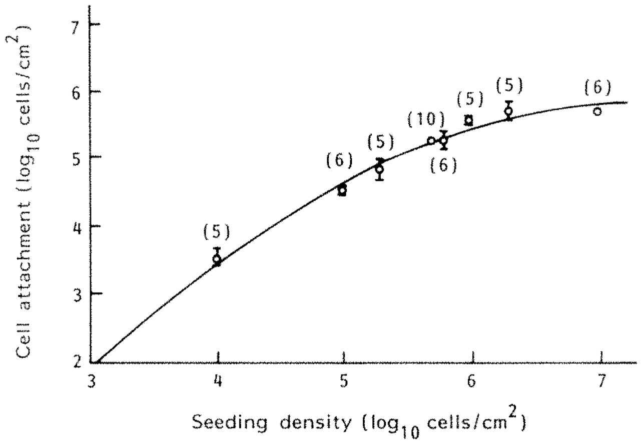

Figure 4 *Mean cell attachment at different seeding densities. Bars are 95 per cent confidence intervals; values in parentheses are numbers of experiments*

Endothelial cell attachment with seeding density

The mean labelling efficiency was 28 per cent (95 per cent c.i. 20–37 per cent). Results have been expressed as the number of cells attaching per square centimetre of dilated vein (*Figure 4*). An almost linear increase in cell attachment occurred up to a seeding density of 2 × 10^6 cells/cm^2, after which little further useful increase in cell attachment occurred. The difference between mean cell attachment at 2 × 10^6 and 1 × 10^7 cells/cm^2 was 6·9 × 10^3 (99 per cent c.i. −2·1 × 10^5 to 2·2 × 10^5) cells/cm^2.

Discussion

PTA is widely used for both peripheral and coronary arterial occlusive disease. Morphological changes occurring in the arterial wall following PTA were initially described in animal models[14–17] and have since been confirmed in human autopsy studies[18]. Endothelial desquamation occurs over the area of the angioplasty, resulting in exposure of subendothelial connective tissue on the luminal surface. An increase in arterial diameter is brought about by a combination of splitting of the intimal atherosclerotic plaque, splitting and stretching of the tunica media, and stretching of the adventitial connective tissue.

Morphological changes in dilated saphenous vein segments of endothelial desquamation and exposure of the subendothelial connective tissue have been described. Changes also occurred in the deeper layers of the vessel wall, with splitting and stretching of the tunica media. It is suggested that the histological changes produced following forcible balloon dilatation of long saphenous vein segments justify the use of this model to study the attachment of endothelial cells to damaged vascular surfaces *in vitro*, although the model is limited as it has no atheromatous plaque, which might alter the surface characteristics after vascular damage.

Endothelial cells possess antithrombotic functions[19–21], which have been postulated to improve patency rates in seeded prosthetic vascular grafts. The endothelial cell monolayer produces fibrinolytic agents such as tissue plasminogen activator[22] and antiplatelet agents such as prostacyclin and endothelium-derived relaxing factor, which also have potent vasodilatory actions[23,24]. Endothelial cells are capable of synthesizing heparin proteoglycans, which may inhibit the smooth muscle proliferation and migration seen in myointimal hyperplasia[25].

Endothelial cell seeding of angioplasty sites may improve patency rates after PTA. Increased production of local antithrombotic agents may reduce the local rethrombosis rate, which has been reported to be as high as 40 per cent following PTA of some femoropopliteal lesions[26]. Late restenosis after PTA of the femoral artery may occur in up to 50 per cent of cases at 5-year follow-up[27,28]. Restenosis occurs because of a mixture of myointimal hyperplasia and atherosclerotic progression[29–32]. Experimental evidence suggests that, in an animal model, the degree of myointimal hyperplasia following arterial injury is reduced in areas covered by regenerating endothelium[33,34]. Thus, re-endothelialization of PTA sites by autologous endothelial seeding seems theoretically advantageous because of the possible reduction of myointimal hyperplasia.

Endothelial cell seeding of prosthetic vascular grafts is hampered by poor cell attachment to the graft surface; this has been partially overcome by the use of surface coatings such as fibronectin or collagen, which improve cell attachment[35–37]. There should be no such problem with endothelial cell seeding of damaged vascular surfaces, as the subendothelial tissue matrix provides an ideal surface for endothelial cell attachment[38,39].

In this study, cell attachment occurred rapidly and was virtually complete by 30 min. At a seeding density of 1×10^5 cells/cm^2 maximal cell attachment was <30 per cent; this contrasts with other studies[35,40], which have shown that cell attachment to fibronectin-coated grafts may reach 50 per cent at 30 min. The differences in these findings may be explained by the use of second or third passage cells in the present experiments, whereas primary cell cultures were used in the studies of endothelial cell attachment to graft surfaces. Cells maintained in tissue culture have been shown to exhibit decreased attachment properties[40].

The effect of seeding density on cell attachment was studied at 30 min, a time that gave near-maximal cell attachment. To achieve confluent endothelial cell coverage of the vein surface (2×10^5 cells/cm^2), a seeding density $>5 \times 10^5$ cells/cm^2 was required. This finding is similar to results obtained for endothelial cell seeding of collagen-coated prosthetic grafts[40]. To achieve such a high seeding density *in vivo*, it will be necessary to amplify harvested endothelial cells in tissue culture before seeding. This implies the use of cells from a second or third passage, as in the present study.

In conclusion, endothelial cell seeding of damaged vascular surfaces may represent a practical clinical application of cell seeding. Seeding time does not need to exceed 30 min but, to obtain confluent endothelial cell coverage, a high seeding density is required.

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References

1. Herring M, Gardner A, Glover J. A single staged technique for seeding vascular grafts with autogenous endothelium. *Surgery* 1978; **84**: 498–504.
2. Budd JS, Allen KE, Hartley G, Bell PRF. The effect of preformed confluent endothelial cell monolayers on the patency and thrombogenicity of small calibre vascular grafts. *Eur J Vasc Surg* 1991; **5**: 397–405.
3. Burkel WE, Vinter DW, Ford JW, Kahn RH, Graham LM, Stanley JC. Sequential studies of healing in endothelial seeded vascular prostheses. *J Surg Res* 1981; **30**: 305–24.
4. Allen BT, Long JA, Clark RE *et al.* Influence of endothelial cell seeding on platelet deposition and patency in small diameter Dacron arterial grafts. *J Vasc Surg* 1984; **1**: 224–33.
5. Fasol R, Zilla P, Deutsch M, Grimm M, Fischlein T, Laufer G. Human endothelial cell seeding: evaluation of its effectiveness by platelet parameters after one year. *J Vasc Surg* 1989; **9**: 432–6.
6. Herring MB, Compton RS, LeGrand DR, Gardner AL, Madison DL, Glover JL. Endothelial seeding of polytetrafluoroethylene popliteal bypasses. *J Vasc Surg* 1987; **6**: 114–18.
7. Ortenwall P, Wadenvik H, Kutti J, Risberg B. Endothelial cell seeding reduces thrombogenicity of Dacron grafts in humans. *J Vasc Surg* 1990; **11**: 403–10.
8. Ortenwall P, Wadenvik H, Risberg B. Reduced platelet deposition on seeded *versus* unseeded segments of expanded polytetrafluoroethylene grafts: clinical observations after a 6-month follow up. *J Vasc Surg* 1989; **10**: 374–80.
9. Herring MB. Endothelial cell seeding. *J Vasc Surg* 1991; **13**: 731–2.
10. Bush HI, Jakubowski JA, Sentissi JM, Culr GR, Hayes JA, Deykin D. Neointimal hyperplasia occurring after carotid endarterectomy in a canine model: effect of endothelial cell seeding *versus* perioperative aspirin. *J Vasc Surg* 1987; **5**: 118–25.
11. Nabel EG, Plautz G, Boyce FM, Stanley JC, Nabel GJ. Recombinant gene expression *in vivo* within endothelial cells of the arterial wall. *Science* 1989; **244**: 1342–4.
12. Jaffe EA, Nachman RL, Becker CG, Minik CR. Culture of human endothelial cells derived from umbilical veins: identification by morphological and immunologic criteria. *J Clin Invest* 1973; **52**: 2745–56.
13. Sharefkin JB, Lather C, Smith M, Rich NM. Endothelial cell labelling with indium-111 oxine as a marker of cell attachment to bioprosthetic surfaces. *J Biomed Mater Res* 1983; **17**: 345–57.
14. Sanborn TA, Faxon DP, Haudenschild C, Gottsman SB, Ryan TJ. The mechanism of transluminal angioplasty: evidence for formation of aneurysms in experimental atherosclerosis. *Circulation* 1983; **68**: 1136–40.
15. Faxon DP, Weber VJ, Haudenschild C, Gottsman SB, McGovern WA, Ryan TJ. Acute effects of transluminal angioplasty in three experimental models of atherosclerosis. *Arteriosclerosis* 1982; **2**: 125–33.
16. Fallon JT. Pathology of arterial lesions amenable to percutaneous transluminal angioplasty. *AJR Am J Roentgenol* 1980; **135**: 913–16.
17. Block PC, Baughman KL, Pasternak RC, Fallon JT. Transluminal angioplasty: correlation of morphologic and angiographic findings in an experimental model. *Circulation* 1980; **61**: 778–85.
18. Block PC, Myler RK, Stertzer S, Fallon JT. Morphology after transluminal angioplasty in human beings. *N Engl J Med* 1981; **305**: 382–5.
19. Weksler BB, Marcus AJ, Jaffe EA. Synthesis of prostaglandin I_2 (prostacyclin) by cultured human and bovine endothelial cells. *Proc Natl Acad Sci U S A* 1977; **74**: 3922–6.
20. Lollar P, Owen WG. Clearance of thrombin from circulation in rabbits by high affinity binding sites on endothelium. *J Clin Invest* 1980; **66**: 1222–30.
21. Esmon CT. The regulation of natural anticoagulant pathways. *Science* 1987; **235**: 1348–52.
22. Nawroth P, Kisiel W, Stern D. The role of endothelium in the homeostatic balance of haemostasis. *Clin Haematol* 1985; **14**: 531–45.
23. Dusting GJ, MacDonald PS. Prostacyclin and vascular function: implications for hypertension and atherosclerosis. *Pharmacol Ther* 1990; **48**: 323–44.
24. Luscher TF, Richard V, Tschudi M, Yang Z, Boulanger C. Endothelial control of vascular tone in large and small coronary arteries. *J Am Coll Cardiol* 1990; **15**: 519–27.
25. Castellot JJ, Addonizio ML, Rosenberg R, Karnovsky MJ. Cultured endothelial cells produce a heparin-like inhibitor of smooth muscle cell growth. *J Cell Biol* 1981; **90**: 372–8.
26. Jorgenson B, Meisner S, Holstein P, Tonnesen KH. Early rethrombosis in femoropopliteal occlusions treated with percutaneous transluminal angioplasty. *Eur J Vasc Surg* 1990; **4**: 149–52.

27. Johnston KW, Rae M, Hogg-Johnston SA *et al.* 5-year results of a prospective study of percutaneous transluminal angioplasty. *Ann Surg* 1987; **206**: 403–13.
28. Gallino A, Mahler F, Probst P, Nachbur B. Percutaneous transluminal angioplasty of the arteries of the lower limbs: a 5 year follow up. *Circulation* 1984; **70**: 619–23.
29. Block PC. Restenosis after percutaneous transluminal coronary angioplasty – anatomic and pathophysiological mechanisms. Strategies for prevention. *Circulation* 1990; **81**(Suppl IV): 2–4.
30. Liu MW, Roubin GS, King SB. Restenosis after coronary angioplasty: potential biologic determinants and role of intimal hyperplasia. *Circulation* 1989; **79**: 1374–87.
31. Fanelli C, Aronoff R. Restenosis following coronary angioplasty. *Am Heart J* 1990; **119**: 357–68.
32. Austin GE, Ratliff NB, Hollman J, Tabei S, Phillips DF. Intimal proliferation of smooth muscle cells as an explanation for recurrent coronary artery stenosis after percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1985; **6**: 369–75.
33. Painter TA. Myointimal hyperplasia: pathogenesis and implications. 2. Animal injury models and mechanical factors. *Artif Organs* 1991; **15**: 103–18.
34. Clowes AW, Reidy MA. Prevention of stenosis after vascular reconstruction: pharmacologic control of intimal hyperplasia. A review. *J Vasc Surg* 1991; **13**: 885–91.
35. Budd JS, Bell PRF, James RFL. Attachment of indium-111 labelled endothelial cells to pretreated polytetrafluoroethylene vascular grafts. *Br J Surg* 1989; **76**: 1259–61.
36. Budd JS, Allen KE, Bell PRF, James RFL. The effect of varying fibronectin concentration on the attachment of endothelial cells to polytetrafluoroethylene vascular grafts. *J Vasc Surg* 1990; **12**: 126–30.
37. Vohra R, Thompson GLJ, Sharma H, Welch M, Walker MG. *In vitro* adherence and kinetics studies of adult human endothelial cell seeded polytetrafluoroethylene and gelatin impregnated Dacron grafts. *Eur J Vasc Surg* 1991; **5**: 93–103.
38. Hoch J, Jarrell BE, Schneider T, Williams SK. Endothelial cell interactions with native surfaces. *Ann Vasc Surg* 1989; **3**: 153–9.
39. Lalka SG, Oelker LM, Malone JM *et al.* Acellular vascular matrix: a natural endothelial cell substrate. *Ann Vasc Surg* 1989; **3**: 108–17.
40. Anderson JS, Price TM, Hanson SR, Harker LA. *In vitro* endothelialization of small calibre vascular grafts. *Surgery* 1987; **101**: 577–86.

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Long-term results of treatment of peptic stricture of the oesophagus with the Angelchik prosthesis

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An Angelchik prosthesis was inserted in 43 patients with a peptic stricture above a hiatus hernia; 16 showed columnar lining of the oesophagus below the stricture. The mean preoperative bore of strictures was 8·7 mm. Within months, and without dilatation, 33 strictures shortened, 35 widened and of these 13 disappeared with a mean bore of 11·7 mm. In the long term, three more strictures resolved but three recurred. Final measurements gave a mean bore of 12·2 mm. The mean follow-up was 3·5 years. Symptomatic and radiological assessments suggested that the prosthesis was less effective when sited in the chest.

The Angelchik antireflux prosthesis was introduced in 1973 for surgical correction of gastro-oesophageal reflux complicating hiatus hernia[1]. Insertion is technically easier than fundoplication and takes about half as long[2]. Four prospective randomized trials that compared Angelchik prosthesis insertion with Nissen fundoplication detected no significant difference in symptomatic or objective control of reflux or in the operative complication rate between the two procedures[2–5]. Nor did a careful sequential trial[6], which emphasized that the two operations were associated with different complications and that late failure may be less common with the Angelchik device.

Anecdotal evidence from small numbers of patients reveals little about the use of the Angelchik prosthesis when peptic stricture complicates gastro-oesophageal reflux. Collective papers[7–14] give the impression that the device was helpful in 77 of 96 patients. Some authors were enthusiastic[2,9], but others discouraged its use in patients with preoperative dysphagia[12,14]. Previous work by the present group[15] has been extended to address this point.

Patients and methods

Between July 1981 and April 1990 one surgeon implanted Angelchik antireflux prostheses into 43 patients (19 men, 24 women) with peptic stricture of the oesophagus. Clinical and radiological assessment was made before operation (43 patients), about 3 months after surgery (43) and at variable intervals thereafter (35). Thirty-five patients had a recent review; five died before this review from unconnected causes (and >30 days after surgery) and three others were not traced.

Clinical assessment

Patients described symptoms of reflux, dysphagia and drug use according to a Visick-type grading. For reflux: 1 means no symptoms; 2, mild symptoms (no treatment); 3, symptoms controlled by medication; and 4, symptoms not controlled. For dysphagia: 1 means no symptoms; 2, solid food sticks less than once weekly; 3, solid food sticks more often than once weekly; and 4, soft food diet required. For drugs used: 1 means none; 2, antacids; 3, intermittent H_2-receptor antagonists; and 4, continuous H_2-receptor antagonists.

Nearly all patients received prolonged treatment with H_2-receptor antagonists before being considered for surgery. Medications were given in dispersed form to avoid impaction on, and irritation of, the stricture. Any dose of non-steroidal anti-inflammatory drug was reduced to as low a level as the patient would tolerate.

Endoscopic assessment

At endoscopy the squamocolumnar junction was identified and oesophagitis graded: 0, normal; 1, erythema; 2, erythema, friability and exudate; 3, erythema, friability and linear erosions; and 4, erythema, friability, exudate, linear erosions and ulceration.

Before insertion of the prosthesis, 14 patients had undergone dilatation of the stricture at least once (over 40 times each in two patients), but the stricture persisted in all cases. Endoscopy was performed after operation only in symptomatic patients for assessment of oesophagitis or for dilatation. Barrett's oesophagus was considered to be present when endoscopy revealed tubular oesophagus below the stricture and biopsy showed that the mucosa was squamous above and columnar below the stricture (11 patients) or when radiology showed the stricture to be $\geqslant 2$ cm above the upper limit of the sphincter segment of the lower oesophagus (five patients).

Radiological assessment

Stricture length and bore. A peptic stricture at the squamocolumnar junction results in a zone of increased resistance to distension, the diameter and length of which can be measured radiologically[16]. The length of the stricture was determined by reference to the known diameter of a swallowed tablet. When the stiffened zone was asymmetric in length, the longest measurement was recorded. The bore of the stricture was assessed using barium sulphate tablets (University College Hospital pharmacy) of increasing size, and taken to be the diameter of the tablet that just passed. Tablets ranged in size from 3·2 to 14·3 mm in diameter in 0·8-mm increments. This technique gave a reproducible estimate of the bore of an oesophageal stricture[17].

Hiatal flow and reflux. Hiatal flow of barium (from the abdomen to the thorax) depends on incompetence of the hiatus. Reflux flow of barium (from the stomach to the oesophagus) indicates breach of the lower oesophageal sphincter[18]. If no reflux was elicited, the patient was examined while toe-touching[16,18]. Hiatal flow and/or reflux was graded: 0 means none; 1, occasional leak just visible in one position; 2, hiatal flow or mild reflux in more than one position; 3, hiatal flow and reflux with flooding of the gullet in one position only; and 4, free hiatal flow with flooding of the gullet in more than one position.

Operative technique

Initially, the technique recommended by Angelchik and Cohen[19] was used. After 1985, crural repair was performed when necessary to reduce the diameter of the hiatus to two fingers' breadth, with the intention of retaining the prosthesis in the abdomen. Dilatation of strictures was omitted at the time of insertion of the Angelchik prosthesis. If indicated, it was deferred until after postoperative radiography.

Ethics

The use of barium sulphate tablets to measure the bore of strictures and the implantation of Angelchik prostheses were originally the subjects of trials approved by the ethical committees of University College and Islington District Hospitals.

Results

The mean(s.d.) age of the patients was 61·1(14·8) (range 28–86) years. The prosthesis remained in the abdomen in the three patients who underwent crural repair. The device did not migrate from abdomen to chest or vice versa between the first and subsequent examinations. In 13 patients the prosthesis was placed above the diaphragm. The mean follow-up was 3·5 years; eight patients were followed for <1 year and five for >7 years.

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Stricture bore and length

Early results. *Figure 1a* shows changes in stricture bore between the preoperative and first postoperative examination 3 months later. In 13 patients the stricture had disappeared and the largest tablet passed without hindrance. These patients had a mean(s.d.) preoperative bore of 10·7(1·9) mm. In 22 patients the stricture improved but did not disappear; mean(s.d.) stricture bores were 7·8(2·3) mm before operation and 10·8(2·1) mm after. In three patients stricture bore was unchanged and in five became narrower.

Changes in length of stricture are shown in *Figure 1b*. No stricture increased in length. There were measurements for 36 patients: ten strictures disappeared, 24 became shorter and two did not change.

Mean values and statistical analysis of these changes are shown in *Table 1*.

Sixteen patients had Barrett's oesophagus. In these, strictures had a mean diameter 1·7 mm smaller than the others, but they also improved following insertion of the device. Early or late regression of the columnar lining was not observed.

Late results. Final measurements gave a mean bore of 12·2 mm. *Figure 2* shows follow-up data for 35 patients. The result at the first postoperative examination was maintained in 13 patients and further improvement occurred in 15, in three of whom the stricture disappeared. There was deterioration in stricture bore in seven patients, the worst case caused by a faulty device which fell off.

Hiatal flow and reflux

Hiatal flow and reflux (referred to for brevity as reflux) was demonstrated in all 43 patients before operation; in 27 no postoperative reflux could be shown. When the prosthesis was placed in the abdomen, reflux ceased in 24 of 30 patients; when it was placed in the chest, reflux ceased in three of 13 ($P < 0{\cdot}01$)[20]. If the Angelchik ring was in the abdomen the latest assessment showed that reflux was the same, or less, in 24 of 28 patients; if it was in the chest, reflux was worse in seven of nine ($P < 0{\cdot}01$)[20]. When the device was in the chest,

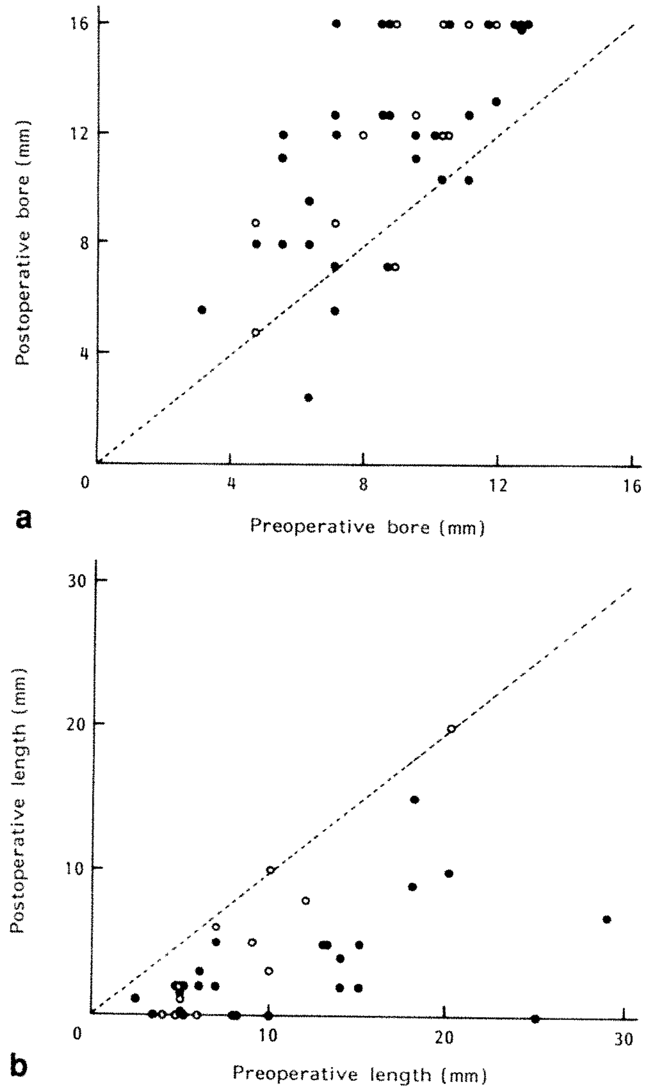

Figure 1 *Change in* **a** *bore and* **b** *length of peptic stricture. Improvement is shown by dots above the diagonal in* **a** *and below it in* **b**. ○, *Patients with prosthesis in the chest;* ●, *patients with prosthesis in the abdomen. See* Table 1

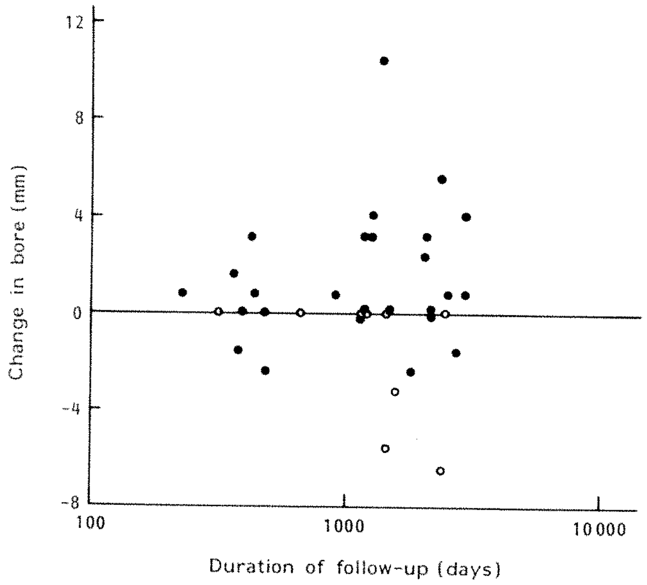

Figure 2 *Long-term follow-up of 35 peptic strictures: changes in bore subsequent to those shown in* Figure 1a. ○, *Nine patients in whom the stricture was not detectable;* ●, *26 in whom it was still detectable at the first follow-up*

Table 1 *Statistical analysis of data in* Figure 1

	Bore (mm)				Length (mm)			
	n	Chest	*n*	Abdomen	*n*	Chest	*n*	Abdomen
Mean preoperative	12	8·85 (7·37–10·32)	31	8·69 (7·72–9·66)	12	8·07 (5·13–11·00)	28	10·57 (7·61–13·54)
Mean postoperative	12	11·82 (9·38–14·25)	31	11·60 (10·21–12·98)	11	5·00 (0·95–9·05)	28	4·70 (2·13–7·26)
Difference								
Preoperative *versus* postoperative	12	−2·97†	31	−2·91*	11	3·44*	25	8·04*
Chest *versus* abdomen		0·06 (−1·90 to 1·78)§				−4·60 (−7·59 to −1·60)‡		

Values in parentheses are 95 per cent confidence intervals. *n*, number of observations. $^*P < 0{\cdot}001$; $^\dagger P < 0{\cdot}002$ (paired *t* test); $^\ddagger P < 0{\cdot}004$; $^\S P$ not significant (two-sample *t* test)

Table 2 *Number of patients with each symptom grade before and after surgery, classified according to location of the prosthesis*

	Grade			
	1	2	3	4
Reflux				
Abdomen				
Preoperative	1	3	12	13
Postoperative	23	5	2	0
Latest	20	8	2	0
Chest				
Preoperative	0	1	3	9
Postoperative	2	6	3	2
Latest	3	1	4	3
Dysphagia				
Abdomen				
Preoperative	0	0	12	18
Postoperative	13	7	4	6
Latest	19	5	3	3
Chest				
Preoperative	0	2	4	7
Postoperative	5	3	2	3
Latest	4	2	3	2
Medication				
Abdomen				
Preoperative	1	2	2	25
Postoperative	21	3	5	0
Latest	20	6	4	0
Chest				
Preoperative	0	1	2	10
Postoperative	3	0	8	2
Latest	3	0	3	5

control of reflux was poorer initially and more likely to deteriorate than when the prosthesis was in the abdomen.

Symptoms of reflux, dysphagia and medication

Table 2 shows numbers of patients classified by grade of symptoms and location of the prosthesis. Numbers are recorded in each category before implantation of the device, at the first postoperative assessment and at the latest assessment. Almost all patients had symptoms of grade 2, 3 or 4 before operation but grade 1 afterwards ($P < 0{\cdot}001$; $\chi^2 = 31{\cdot}11$ for reflux, 22·76 for dysphagia, 30·75 for medication, 1 d.f., 2 × 2 contingency table combining numbers for grades 2, 3 and 4 in this and subsequent tests). No significant deterioration occurred between the first postoperative and the latest assessment. The results were superior when the prosthesis was placed in the abdomen both for symptoms of reflux and need for drug treatment ($\chi^2 = 14{\cdot}00$ for reflux, 8·92 for medication, 1 d.f., $P < 0{\cdot}01$).

Discussion

An indication of the severity of oesophageal strictures is given by length and bore, but only Bennett's group[21,22] and Edwards *et al.*[17] have made measurements. Two points particularly deserve discussion:

1. A highly significant increase in the bore and decrease in the length of oesophageal strictures occurred by the time of the initial postoperative examination – an improvement that cannot be attributed to oesophageal bougienage because it was not performed during this time. Implantation of the prosthesis can cause complete resolution of peptic strictures of the oesophagus (13 of 43 in the present series). This conclusion is corroborated by the fate of one patient whose prosthesis fell off and whose stricture recurred. Improvement 3 months after operation usually gave a good prediction of the long-term result.
2. Objective radiology and subjective symptom grades suggest that the prosthesis works less well when it is sited in the chest, but even in this situation it was clearly beneficial. The device can enter the chest only if the crura are wide enough (i.e. in the worst hernias) and inferior results thus cannot be blamed on the position of the prosthesis alone.

Dysphagia is difficult to quantify by subjective means; until the oesophagus is completely impassable, the symptom can be avoided by a liquid diet. The reported frequency of dysphagia thus depends on dietary discretion in addition to the bore of the stricture. Implantation of an Angelchik prosthesis may cause a different kind of dysphagia from that caused by stricture, but the subjective grades reveal a similar pattern to objective measurements of stricture bore. In the present series, implanting a prosthesis usually had a beneficial and long-lasting effect: most strictures improved or disappeared. This modest success, and a lack of complications, may indicate that an authoritarian view that the device should never be used[23,24] is mistaken and may have inappropriately discouraged surgeons.

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References

1. Angelchik J-P, Cohen R. A new surgical procedure for treatment of gastroesophageal reflux and hiatal hernia. *Surg Gynecol Obstet* 1979; **148**: 246–8.
2. Gear MWL, Gillison EW, Dowling BL. Randomized prospective trial of the Angelchik anti-reflux prosthesis. *Br J Surg* 1984; **71**: 681–3.
3. Gourley GR, Pellet JR, Ulysses B, Li K, Adkins WN Jr. A prospective, randomized, double-blind study of gastroesophageal reflux surgery in pediatric-sized developmentally disabled patients: Nissen fundoplication *versus* Angelchik prosthesis. *J Pediatr Gastroenterol Nutr* 1986; **5**: 52–61.
4. Stuart RC, Dawson K, Keeling P, Byrne PJ, Hennessy TPJ. A prospective randomized trial of Angelchik prosthesis *versus* Nissen fundoplication. *Br J Surg* 1989; **76**: 86–9.
5. Kmiot WA, Kirby RM, Akinola D, Temple JG. Prospective randomized trial of Nissen fundoplication and Angelchik prosthesis in the surgical treatment of medically refractory gastro-oesophageal reflux disease. *Br J Surg* 1991; **78**: 1181–4.
6. Deakin M, Mayer D, Temple JG. Surgery for gastro-oesophageal reflux: the Angelchik prosthesis compared to the floppy Nissen fundoplication. Two-year follow-up study and a five-year evaluation of the Angelchik prosthesis. *Ann R Coll Surg Engl* 1989; **71**: 249–52.
7. Starling JR, Reichelderfer MO, Pellett JR, Belzer FO. Treatment of symptomatic gastroesophageal reflux using the Angelchik prosthesis. *Ann Surg* 1982; **195**: 686–91.
8. Kozarek RA, Phelps JE, Sanowski RA, Grobe JL, Fredell HC. An antireflux prosthesis in the treatment of gastro-esophageal reflux. *Ann Intern Med* 1983; **98**: 310–15.
9. Malik MA, Tahir MA, Sawyna V. Angelchik prosthesis. *Surgery* 1984; **95**: 126.
10. Temple JG, Taylor TV, Alexander-Williams J. A simple operative prosthetic treatment for gastro-oesophageal reflux. *J R Coll Surg Edinb* 1984; **29**: 16–17.
11. Durrans D, Armstrong CP, Taylor TV. The Angelchik anti-reflux prosthesis – some reservations. *Br J Surg* 1985; **72**: 525–7.
12. Wale RJ, Royston CMS, Bennett JR, Buckton GK. Prospective study of the Angelchik anti-reflux prosthesis. *Br J Surg* 1985; **72**: 520–4.
13. Goldberg JA, Bell G, Morrice JJ, Davidson PM. The Angelchik prosthesis: experience with the anti-reflux device. *J R Coll Surg Edinb* 1987; **32**: 205–8.
14. Timoney AG, Welfare MR, Kelly JM. The Angelchik antireflux device: a 5-year experience. *Ann R Coll Surg Engl* 1990; **72**: 185–7.
15. Wyllie JH, Edwards DAW. A quantitative assessment of results with the Angelchik prosthesis. *Ann R Coll Surg Engl* 1985; **67**: 216–21.
16. Edwards DAW. Techniques in radiological examination of the oesophagus. In: Watson A, Celestin LR, eds. *Disorders of the Oesophagus*. London: Pitman, 1984: 13–23.

17. Edwards DAW, Williams AR, Wyllie JH. Radiographic measurement of oesophageal stricture size. *Gut* 1982; **23**: A448.
18. Edwards DAW. Diaphragm and hiatus hernia. In: Shanks SC, Kerley P, eds. *Textbook of X-ray Diagnosis*. 4th ed. London: HK Lewis, 1969: 266–319.
19. Angelchik J-P, Cohen R. A silicone prosthesis for gastro-esophageal reflux: long-term results. *Contemporary Surgery* 1985; **26**: 29–32.
20. Hypergeometrical distribution – fourfold table test. In: Diem K, ed. *Documenta Geigy Scientific Tables*. 6th ed. New York: Geigy Pharmaceuticals, 1962: 109–23.
21. Dyet JF, Bennett JR, Buckton GK, Ashworth D. The radiological measurement of oesophageal stricture diameter. *Clin Radiol* 1983; **34**: 647–9.
22. Cox JGC, Winter JK, Maslin SC *et al.* Balloon or bougie for dilatation of benign oesophageal stricture? An interim report of a randomised controlled trial. *Gut* 1988; **29**: 1741–7.
23. Editorial. Angelchik antireflux prosthesis. *Lancet* 1985; **ii**: 987.
24. Editorial. Angelchik revisited, lessons for the introduction of new operations. *Lancet* 1992; **339**: 340.

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Case report

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Cutaneous metastasis from a malignant fibrous histiocytoma to a limb skin graft donor site

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Soft tissue sarcomas are rare and account for fewer than 1 per cent of all malignant tumours[1]. Malignant fibrous histiocytoma represents approximately one-third of these and probably originates from primitive mesenchymal precursor cells. These tumours often remain locally invasive, but haematogenous spread is recognized in 30 per cent of cases and lymphatic in 12 per cent[2].

Malignant fibrous histiocytomas metastasizing to the scalp and trunk have been described[2,3]. A case of metastasis to a contralateral lower-limb skin graft donor site is reported and possible modes of dissemination discussed.

Case report

A 65-year-old man presented with a painless swelling on the right upper arm that had been present for 15 years. In the 6 months before presentation, the swelling had rapidly enlarged and ulcerated. Wide local excision was performed and the resulting defect was covered with a split skin graft harvested from the left thigh. Results of baseline chest radiography, haematological and biochemical screening were normal. Histologically the tumour was composed of bundles of pleomorphic spindle cells arranged in storiform pattern with numerous mitotic figures, some being atypical. The morphology of the cells and their arrangement indicated a diagnosis of malignant fibrous histiocytoma. Sections of the deep margin showed that the tumour excision was incomplete.

Further excision at this unit achieved apparent histological clearance, a split skin graft successfully healing the defect. However, 4 weeks later there was evidence of local recurrence and dyspnoea at rest. Chest radiography revealed multiple discrete lesions suspicious of pulmonary metastases. The original skin graft donor site also contained a firm nodular lesion 2 cm in diameter that had ulcerated through the overlying skin (*Figure 1*).

Further wide excision was undertaken and the donor site lesion excised. Histological examination confirmed local recurrence of the histiocytoma. The nodule at the donor site was composed of similar portions of malignant fibrous histiocytoma and inflamed granulation tissue. The patient's condition deteriorated and he died from disseminated malignancy 6 weeks later.

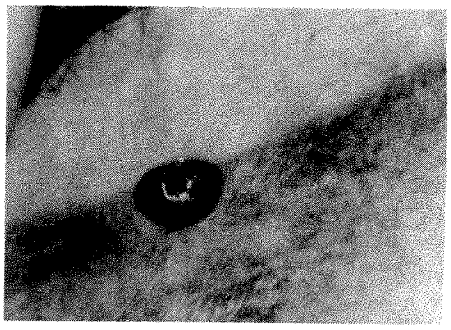

Figure 1 *Cutaneous metastasis of tumour to the donor site of the left thigh*

Discussion

Malignant fibrous histiocytoma has a 60–80 per cent 5-year survival rate[1,4]. The patient reported clearly had aggressive disease, shown by the widespread metastases and local recurrence. Pulmonary metastases are well documented; cutaneous metastases have been observed infrequently and in some cases only in autopsy material[2]. Cutaneous limb metastases have not been previously reported.

The mode of spread of tumour to the donor site is unclear: haematogenous spread is a possibility. Endothelial cells in granulation tissue are known to be 'sticky', allowing contact with leucocytes, for example. This case may represent haematogenous seeding within the highly vascularized donor site. The occurrence of tumour at the donor site also raises the possibility of iatrogenic spread. A donor site theoretically presents a suitable environment for tumour cells to thrive, and a deposit of tumour from a contaminated glove remains possible[5]. This case is the first to illustrate distant cutaneous metastasis to a limb from a malignant fibrous histiocytoma. To avoid the possibility of direct tumour inoculation from the surgeon's gloves, we would recommend either harvesting the skin before handling the tumour or changing gloves once the latter is resected.

Acknowledgements

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References

1. Potter DA, Kinsella T, Glatstein E *et al.* High grade soft tissue sarcomas of the extremities. *Cancer* 1986; **58**: 190–205.
2. Weiss SW, Enzinger FM. Malignant fibrous histiocytoma. An analysis of 200 cases. *Cancer* 1978; **41**: 2250–66.
3. Kearney MM, Soule EH, Ivins JC. Malignant fibrous histiocytoma. A retrospective study of 167 cases. *Cancer* 1980; **45**: 167–78.
4. Serpell JW, Ball ABS, Robinson MH. Factors influencing local recurrence and survival in patients with soft tissue sarcomas of the upper limb. *Br J Surg* 1991; **78**: 1368–72.
5. Robbins SL, Cotran RS, Kumar V. *Pathological Basis of Disease*. Philadelphia, Pennsylvania: WB Saunders, 1984: 226.

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Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial

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A prospective randomized trial of 67 patients undergoing oesophagectomy by either a transhiatal approach or right-sided thoracotomy was conducted over a 40-month period. In 32 patients the approach was transhiatal and 35 had a thoracotomy; the groups were well matched before operation. There were two hospital deaths in patients having the transhiatal oesophagectomy and three in those undergoing thoracotomy. Blood transfusion, intensive care stay and overall time of hospitalization were not significantly different between the two groups. There was no difference in the postoperative morbidity rate and, in particular, the incidences of pulmonary complications were similar (19 per cent for transhiatal oesophagectomy, 20 per cent for thoracotomy) with anastomotic fistula in 6 and 9 per cent respectively. The median (range) operating time was significantly longer in patients having thoracotomy (6 (3·5–9·5) versus 4 (3–8) h). Long-term survival was unaffected by the type of operation performed or addition of preoperative chemotherapy or radiotherapy. Nodal status was a significant prognostic factor within but not between the two groups. It is concluded that oesophagectomy by a transhiatal route or right thoracotomy are equally effective surgical options for treatment of squamous cell oesophageal cancer.

Controversy still exists as to the optimal surgical approach to oesophagectomy for patients with oesophageal carcinoma. The two main operations currently advocated are transhiatal oesophagectomy with cervical anastomosis and oesophagectomy with right-sided thoracotomy. The transhiatal approach was first reported in 1931 and again 5 years later by Grey Turner[1,2], but has been more recently popularized by Orringer and colleagues[3–5]. Oesophagectomy with right-sided thoracotomy has had a number of advocates over the years since Lewis[6] in 1946 and Tanner[7] in 1947 reported experience using an abdominal and right thoracotomy approach.

Proponents of the transhiatal route argue that it avoids a thoracotomy and the attendant respiratory complications, any sepsis from a disrupted anastomosis also being less serious in the cervical region[8]. Those favouring thoracotomy and intrathoracic oesophageal anastomosis emphasize the ability to clear the tumour and involved lymph nodes, and the relative safety of the procedure if other mediastinal structures are adherent[9–12]. Few reports comparing the two methods have been published[13–16] and no prospective randomized study exists. This paper reports such a study, comparing the transhiatal approach with thoracotomy.

Patients and methods

Between February 1988 and May 1991, 198 patients presented to the Department of Digestive Surgery, Pontchaillou Hospital, with cancer of the oesophagus. Of these 198, 108 were initially eligible for inclusion in the trial; the eligibility and exclusion criteria are shown in *Table 1*. On the basis of these criteria, 27 patients were excluded after subsequent investigation: seven refused surgery, four had metastatic spread, five oesophagotracheal fistula, two associated pharyngeal cancer, four were unsuitable for anaesthesia, one died before surgery, one had chemotherapy before enrolment, one had cervical oesophageal cancer and two had an adenocarcinoma. A further 14 patients were found at the time of operation to be unsuitable for randomization: eight had disseminated carcinoma and in six an alternative procedure was used because of unexpected extensive invasion of adjacent structures by tumour.

This left 67 patients to be randomized to one of the two treatments. One group of 32 patients underwent transhiatal oesophagectomy and the other of 35 oesophagectomy with a right thoracotomy. Patient and tumour characteristics are shown in *Table 2*. Presenting symptoms were similar in the two groups. Before operation all patients underwent routine haematological tests for haemoglobin level, haematocrit, white blood cell count, total serum proteins and albumin determination. Chest radiography, barium meal studies, oesophageal endoscopy with biopsy of oesophageal lesion, and tests of respiratory function and blood gases were also performed.

The operative technique of transhiatal oesophagectomy was similar to that described by Orringer and Sloan[3], while patients undergoing thoracotomy were treated using the method already published from

Table 1 *Eligibility and exclusion criteria*

Eligibility criteria
1. Squamous cell carcinoma of the oesophagus
2. Age <70 years
3. Karnofsky score >60 or WHO performance status <2
4. Life expectancy estimated >3 months
5. No previous treatment for cancer
6. Acceptance of the trial and randomization by the patient

Exclusion criteria
1. Carcinoma of the cervical oesophagus
2. Weight loss >15% of initial weight
3. Malignant oesophagotracheal fistula or tracheal mucosal involvement
4. Preoperative evidence of extraoesophageal spread (liver metastases, subclavicular node or recurrent laryngeal nerve paralysis)
5. Past history of cancer (except carcinoma of the skin or cervix treated curatively and ear, nose and throat cancer treated without evidence of recurrence for at least 5 years)
6. Renal insufficiency (serum creatinine >120 μmol/l) or liver insufficiency (prothrombin time <60%, transaminases up >threefold); chronic pulmonary or cardiac insufficiencies
7. Uncontrolled sepsis
8. WBCs <2 × 10^9/l or platelets <120 × 10^9/l
9. Radiotherapy or chemotherapy received in another institution for treatment of oesophageal carcinoma
10. Follow-up not possible

WHO, World Health Organization; WBC, white blood cell

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Table 2 *Patient and tumour characteristics for oesophagectomy by the two approaches*

	Transhiatal approach ($n = 32$)	Right thoracotomy ($n = 35$)
Age (years)*	57·4(7·9)	57·4(8·4)
Sex ratio (F:M)	1:31	2:33
Smokers (%)	81	85
Alcoholic (%)	90	88
Dysphagia		
Frequency (%)	81	88
Duration (months)*	2·5	3·1
Weight loss		
Frequency (%)	62	65
Amount (kg)*	5·2(3·31)	5·0(2·39)
Serum albumin (g/l)*	41·6(3·44)	40·0(3·23)
Barium swallow		
Tumour length (cm)*	5·3(1·33)	4·9(1·73)
Minimum calibre of stenosis (mm)*	9·1(4·49)	12·1(6·00)
Endoscopy		
Occlusive stenosis	3	8
Multifocal lesion	0	0
Exuberant lesion	25	23
Ulcerated lesion	19	22
Infiltrated lesion	13	18
Distance to dental arch (cm)*	29·6	29·6
Pathology		
Well differentiated	25	27†
Poorly differentiated	6	2
Undifferentiated	1	6
Location		
Upper third	2	0
Middle third	18	19
Lower third	12	16

*Values are mean(s.d.). †Includes one carcinoma with both squamous cell and adenocarcinoma elements. There were no significant differences between the two groups

this centre[17]. All patients had a feeding jejunostomy inserted during the operation. Operating time, transfusion requirement, tumour stage, and postoperative morbidity and mortality rates were recorded. Three patients originally randomized to the transhiatal approach were converted to a right thoracotomy because it was not possible to remove the tumour safely by the former route.

Follow-up was performed in July 1991 so at least 2 months had elapsed since surgery for all patients. Data were analysed using Kaplan–Meier life-table analysis[18] and Student's t test with Yates' correction[19].

Results

Operative data

Patients who underwent oesophagectomy by the transhiatal approach required a median operating time of 4 (range 3–8) h compared with that of those undergoing thoracotomy of 6 (range 3·5–9·5) h. Much of the additional time required for the latter procedure involved repositioning and redraping of the patient before the thoracotomy. The median (range) transfusion requirements for the transhiatal approach and thoracotomy were not significantly different at 2·3 (1–10) *versus* 2·3 (0–8) units respectively. In each group ten patients required no transfusion during the operative or perioperative periods.

In patients undergoing transhiatal oesophagectomy the pleura was opened in four cases and the spleen damaged but preserved in three; one splenectomy was performed for a splenic infarction and perforation of the tumour occurred in one patient. In patients submitted to thoracotomy, splenic damage occurred once and the tumour was perforated in one case. Tumour node metastasis staging at time of surgery is summarized in *Table 3*.

Postoperative data

The median (range) time spent in the intensive care unit after surgery was not significantly different between the transhiatal approach and thoracotomy: 9·2 (2–45) *versus* 8·6 (2–60) days. The overall period of hospitalization was also similar: median (range) 20·5 (14–57) *versus* 18·0 (3–80) days respectively.

Hospital morbidity is summarized in *Table 4* for the two groups, which were not significantly different in this respect. There were two hospital deaths in patients undergoing transhiatal oesophagectomy (from pulmonary embolus on day 60 and myocardial infarction on day 15) and three deaths in those receiving thoracotomy (from adult respiratory distress syndrome on day 13, pneumonia on day 80 and pulmonary embolus on day 3).

Late complications

Three patients receiving transhiatal oesophagectomy had anastomoses that required dilatation, at 3, 6 and 9 months respectively. Additionally there were two fistulas in patients who had mechanical anastomoses with an additional stenosis at 2 months after surgery in this group. In patients undergoing thoracotomy all anastomoses were mechanical, and in three non-lethal fistula developed without stenosis. However, two additional patients required dilatation for recurrent disease.

Death had occurred in 16 patients at the time of review in those operated on by the transhiatal approach, from metastatic disease in seven patients, recurrent mediastinal disease in five and other causes in four. In patients receiving thoracotomy, death at follow-up was from metastatic disease in ten, mediastinal recurrence in nine and other causes in three. The number and causes of death in each group were not significantly different.

Survival

The overall survival for each group was not significantly different (*Figure 1*). The absence of histologically positive lymph nodes did not cause any difference in survival between groups (*Figure 2*). However, when the subgroup of patients

Table 3 *Tumour node metastasis classification at time of oesophagectomy by the two approaches*

Classification	Stage	Transhiatal approach	Right thoracotomy
$T_{1/2}N_0M_0$	I or II	19	12
		5	1
T_2N_{1-3}	III	0	3
T_3N_0		4	3
T_3N_{1-3}		4	11
Palliative surgery*		4	6

*Macroscopic malignant tumour left in the mediastinum or abdomen

Table 4 *Hospital morbidity following each procedure*

	Transhiatal approach ($n = 18$; 56%)	Right thoracotomy ($n = 16$; 46%)
Pulmonary infection	6 (19)	7 (20)
Pleural effusion	11 (34)	4 (11)
Anastomotic leakage	2 (6)	3 (9)
Recurrent laryngeal nerve paralysis	1 (3)	1 (3)
Thoracic bleeding	0 (0)	1 (3)
Cervical abscess without fistula	2 (6)	—
Gastroplasty necrosis	1 (3)	0 (0)
Jejunostomy leak	1 (3)	0 (0)
Other	3 (9)	5 (14)

Values in parentheses are percentages. There were no significant differences between the two groups

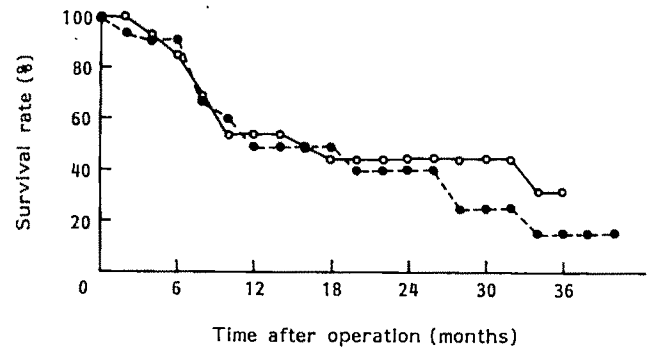

Figure 1 *Survival curves for patients undergoing oesophagectomy by a transhiatal approach* (○) *or right thoracotomy* (●). *There was no significant difference in survival between the two groups*

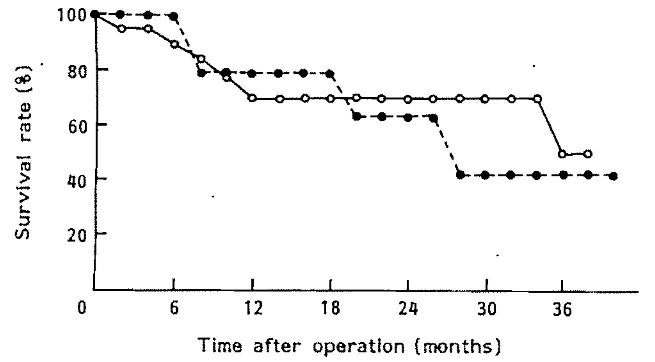

Figure 2 *Survival curves for patients without nodal involvement* (*stage I disease*) *undergoing oesophagectomy by a transhiatal approach* (○) *or right thoracotomy* (●). *There was no significant difference in survival between the two groups*

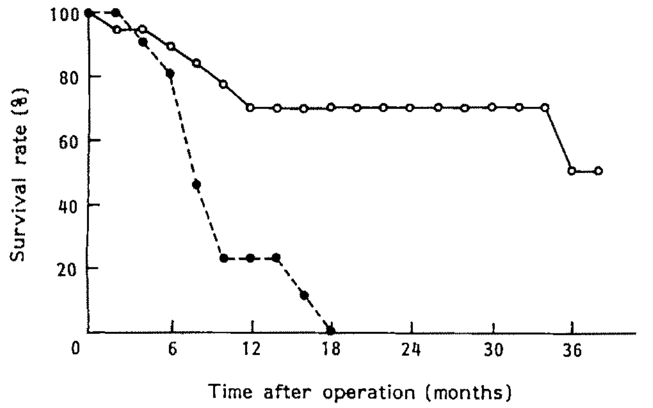

Figure 3 *Survival curves for patients undergoing oesophagectomy by a transhiatal approach with stage I or II* (○) versus *stage III* (●) *disease. Earlier disease stages were associated with significantly better survival* (P < *0·001*)

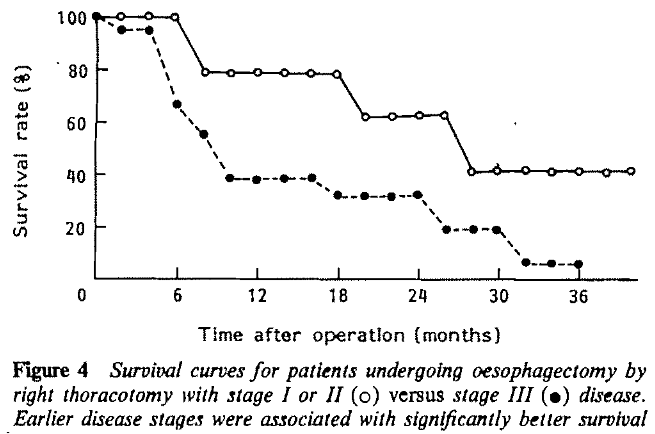

Figure 4 *Survival curves for patients undergoing oesophagectomy by right thoracotomy with stage I or II* (○) versus *stage III* (●) *disease. Earlier disease stages were associated with significantly better survival* (P < *0·02*)

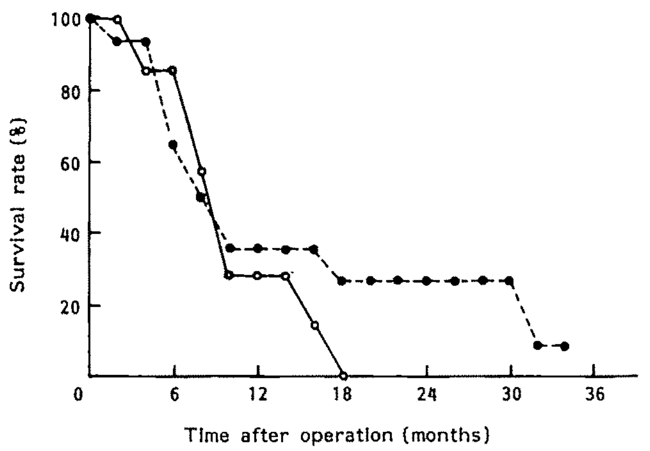

Figure 5 *Survival curves for patients with nodal involvement* (*stage III disease*) *undergoing oesophagectomy by a transhiatal approach* (○) *or right thoracotomy* (●). *There was no significant difference in survival between the two groups*

undergoing transhiatal oesophagectomy and without nodal involvement was compared with that with such involvement, a significant difference in survival was found ($P < 0{\cdot}001$; *Figure 3*); this was also the case within those receiving thoracotomy ($P < 0{\cdot}02$; *Figure 4*). *Figure 5* shows that the overall survival in node-positive patients undergoing either operation was not significantly different between groups.

Discussion

Despite reports advocating one form of oesophagectomy in preference to another[20–26], no randomized prospective study has addressed the question of the optimal surgical approach. The few reports that have considered the two techniques within the same institution are retrospective and contradictory. Shahian *et al.*[16] and Muller and colleagues[24] reported an improved morbidity rate with a right thoracotomy whereas Fok *et al.*[13] showed no difference in outcome for this procedure compared with transhiatal oesophagectomy. Sixty-seven patients were randomized into two groups in the present study, receiving either transhiatal oesophagectomy or thoracotomy; within the former group 9 per cent of procedures had to be converted to thoracotomy because of adherence to mediastinal structures found at operation. This compares with a conversion rate of 4 per cent reported by Orringer[5].

Despite the alleged advantage of the transhiatal route in minimizing respiratory complications[3], no difference was found between the postoperative morbidity or mortality rates for the two groups. There were also similar blood transfusion requirements and hospital stay. It appears that any respiratory advantage conferred by transhiatal oesophagectomy is probably theoretical and at best slight, and should not be an over-riding consideration in the proposed surgical approach.

The major difference between the two groups was a longer operation time for patients having thoracotomy. This is to be expected unless a combined synchronous approach is used[20]. The advantage of a shorter operating time needs to be balanced with the need for two surgical teams and the relative difficulty of such an approach.

Initial reports suggested an associated hospital mortality rate following oesophagectomy of between 25 and 40 per cent[26–31]. More recent studies describe rates of around 5 per cent[17]. The present series contained five deaths, none directly related to complications resulting from imperfect surgical technique. Intrathoracic anastomotic leaks are a particularly serious complication reported to have a mortality rate of over 50 per cent[31–33] and are one of the principal dangers of right thoracotomy. On the other hand, necrosis of the gastroplasty is reported to occur in 5 per cent of cases following transhiatal oesophagectomy, with a 97 per cent mortality rate[34].

Neither complication caused a fatality in the present group of patients.

Advocates of thoracotomy have suggested that the procedure permits a more complete clearance of involved nodes (both macroscopic and microscopic[9,10,12,29,35]) and, therefore, an improved survival. It is well known that there is a significant difference in long-term survival depending on lymph node involvement[35]. This difference has again been shown to be significant between stage I and III disease for both approaches. The difference seemed more significant in patients undergoing transhiatal oesophagectomy, but in that group there was a bias created by the fact that many patients had no involved nodes.

All previous reports comparing right thoracotomy and transhiatal oesophagectomy have suffered from being retrospective and often not contemporaneous[14,36,37]. This is an understandable problem as few institutions see a sufficient number of cases annually to start an adequately large prospective randomized trial. This study was able to document prospectively a group of patients with squamous cell carcinoma of the oesophagus undergoing either of the approaches over a short 40-month period. During this time no significant changes in intensive care treatment and preoperative or postoperative management occurred. The results indicate that no advantage exists in favour of either surgical approach. Both offer adequate management, albeit doing little to alter the dismal prognosis of the disease. At the present time, advances in the management of oesophageal carcinoma are likely to come only from earlier detection and/or improved screening. Surgeons should be competent in all forms of oesophageal resection and bypass, and efforts should be directed at reduced stenosis and leak rates for all procedures rather than pursuing a single operative intervention for all patients.

References

1. Grey Turner G. Some experiences in the surgery of the esophagus. *N Engl J Med* 1931; **205**: 657.
2. Grey Turner G. Carcinoma of the oesophagus: the question of its treatment by surgery. *Lancet* 1936; **i**: 67–72, 130–4.
3. Orringer MB, Sloan H. Esophagectomy without thoracotomy. *J Thorac Cardiovasc Surg* 1978; **76**: 643–54.
4. Orringer MB, Orringer JS. Esophagectomy without thoracotomy: a dangerous operation? *J Thorac Cardiovasc Surg* 1983; **85**: 72–80.
5. Orringer MB. Transhiatal esophagectomy without thoracotomy for carcinoma of the thoracic esophagus. *Ann Surg* 1984; **200**: 282–7.
6. Lewis I. The surgical treatment of carcinoma of the esophagus with special reference to a new operation for growths of the middle third. *Br J Surg* 1946; **34**: 18–31.
7. Tanner NC. The present position of carcinoma of the esophagus. *Postgrad Med J* 1947; **23**: 109–39.
8. Ellis FH. Treatment of carcinoma of the esophagus or cardia. *Mayo Clin Proc* 1989; **64**: 945–55.
9. Ishida K, Mori S, Okamoto K *et al.* Results of extended dissection of lymph nodes in operation for thoracic oesophageal cancer. *World Congress of the International Society for Diseases of the Esophagus*. Munich, September 1986.
10. Peracchia A, Bardini R, Castoro C *et al.* La lymphadénectomie dans le traitement du cancer de l'oesophage intrathoracique. A propos de l'étude de 240 cas. *Ann Chir* 1990; **44**: 9–17.
11. Sasaki K, Muto T, Tanaka O, Soga J. The significance of systematic lymphadenectomy for thoracic oesophageal carcinoma. *World Congress of the International Society for Diseases of the Esophagus*. Munich, September 1986.
12. Skinner DB. *En bloc* resection for neoplasms of the esophagus and cardia. *J Thorac Cardiovasc Surg* 1983; **85**: 59–71.
13. Fok M, Siu KF, Wong J. A comparison of transhiatal and transthoracic resection for carcinoma of the thoracic esophagus. *Am J Surg* 1989; **158**: 414–19.
14. Garvin PJ, Kaminski DL. Extrathoracic esophagectomy in the treatment of esophageal cancer. *Am J Surg* 1980; **140**: 771–8.
15. Hankins JR, Attar S, Coughlin TR *et al.* Carcinoma of the esophagus: a comparison of the results of transhiatal *versus* transthoracic resection. *Ann Thorac Surg* 1989; **47**: 700–5.
16. Shahian DM, Neptune WB, Ellis FH Jr, Watkins E. Transthoracic *versus* extrathoracic esophagectomy: mortality, morbidity, and long-term survival. *Ann Thorac Surg* 1986; **41**: 237–46.
17. Launois B, Paul JL, Lygidakis NJ *et al.* Results of the surgical treatment of carcinoma of the oesophagus. *Surg Gynecol Obstet* 1983; **156**: 753–60.
18. Hill C, Benhamou E, Rey A. Construction d'une courbe de survie. *Revue du Praticien* 1983; **33**: 1041–50, 1059–66.
19. Gossett WS (Student). *Biometrika* 1908; **6**: 1.
20. Royston CMS, Dowling BL. A combined synchronous technique for the McKeown three phase oesophagectomy. *Br J Surg* 1976; **63**: 122–4.
21. Gotley DC, Beard J, Cooper MJ, Britton DC, Williamson RCN. Abdominocervical (transhiatal) oesophagectomy in the management of oesophageal carcinoma. *Br J Surg* 1990; **77**: 815–19.
22. Gupta NM. Transhiatal oesophagectomy. *Acta Chirurgica Scandinavica* 1990; **156**: 149–53.
23. Mannell A, Becker PJ. Evaluation of the results of oesophagectomy for oesophageal cancer. *Br J Surg* 1991; **78**: 36–40.
24. Muller JM, Erasmi H, Stelzner M, Zieren U, Pichlmaier H. Surgical therapy of oesophageal carcinoma. *Br J Surg* 1990; **77**: 845–57.
25. Peracchia A, Bardini R, Segalin A *et al.* L'oesophagectomie sans thoracotomie comme traitement du cancer de l'oesophage. *Chirurgie* 1990; **116**: 762–7.
26. Muller JM, Zieren U, Wolters U, Pichlmaier H. Results of esophagectomy and gastric bypass for cancer of the esophagus. *Hepatogastroenterology* 1989; **36**: 552–8.
27. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: I. A critical review of surgery. *Br J Surg* 1980; **67**: 381–90.
28. Giuli R, Gignoux M. Treatment of carcinoma of the esophagus. Retrospective study of 2400 patients. *Ann Surg* 1980; **192**: 44–52.
29. Logan A. The surgical treatment of carcinoma of the esophagus and cardia. *J Thorac Cardiovasc Surg* 1963; **46**: 150–61.
30. Lortat-Jacob JL, Maillard JN, Richard CA, Fekete F, Launois B. Surgical treatment of cancer of the oesophagus. *Br J Clin Pract* 1970; **24**: 13–16.
31. Maillard JN, Launois B, De Lagausie P, Lellouch J, Lortat-Jacob JL. Cause of leakage at the site of anastomosis after esophagogastric resection for carcinoma. *Surg Gynecol Obstet* 1969; **129**: 1014–18.
32. Chassin JL. Stapling technique for esophagogastrostomy after esophagogastric resection. *Am J Surg* 1978; **136**: 399–404.
33. Lorentz T, Fok M, Wong J. Anastomotic leakage after resection and bypass for esophageal cancer: lessons learned from the past. *World J Surg* 1989; **13**: 472–7.
34. Moorehead RJ, Wong J. Gangrene in esophageal substitutes after resection and by-pass procedures for carcinoma of the esophagus. *Hepatogastroenterology* 1990; **37**: 364–7.
35. Akiyama H, Tsurumaru M, Kawamura T, Ono Y. Principles of surgical treatment for carcinoma of the esophagus. Analysis of lymph node involvement. *Ann Surg* 1981; **194**: 438–46.
36. Caracci B, Garvin P, Kaminski DL. Surgical therapy of advanced esophageal cancer: a critical appraisal. *Am J Surg* 1983; **146**: 703–7.
37. Steiger Z, Wilson RF. Comparison of results of esophagectomy with or without a thoracotomy. *Surg Gynecol Obstet* 1981; **153**: 653–6.

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Intragastric bile acid and symptoms in patients with an intrathoracic stomach after oesophagectomy

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Bile acid concentration and symptoms were evaluated in 24 patients after total oesophagectomy and gastric pull-up. Patients were randomly allocated to receive pyloroplasty or not. After operation all were followed for a minimum of 6 months. Bile acid concentration in the gastric juice was estimated. The mean(s.d.) bile acid concentration 6 months after surgery was similar in patients with and without pyloroplasty (34·9(30·1) and 25·0(24·2) mg/dl respectively). Postprandial discomfort and bilious eructations were the two most commonly observed symptoms in both groups. Other features noted were vomiting, anaemia and anorexia. These did not however seem to be related to intragastric bile acid concentration of individual patients in either group and occurred irrespective of whether pyloroplasty was performed or not.

Total oesophagectomy with gastric pull-up through the posterior mediastinum is a standard procedure for malignancy and intractable corrosive stricture of the oesophagus. Because total vagotomy and resultant gastric stasis is an inevitable consequence of this operation, some surgeons routinely perform pyloroplasty[1–3]; others believe that the intrathoracic stomach empties well even without such a procedure[4].

It is also believed that pyloric denervation leads to increased duodenogastric reflux of bile[5]. Such reflux following gastrojejunostomy or gastrectomy has potentially harmful effects on the gastric mucosa[6]: it is supposed to be responsible for 'biliary gastritis', intestinal metaplasia and mucosal hyperplasia[7]. Unfortunately, little is known about bile reflux in the intrathoracic stomach.

The present study was therefore undertaken to detect duodenogastric reflux by measuring bile acid concentration in the intrathoracic stomach and to correlate this with the clinical symptoms of patients after oesophagectomy.

Patients and methods

Between July 1988 and June 1990, 100 patients with operable benign (15 patients) or malignant (85) lesions of the oesophagus were managed surgically. All underwent surgery after thorough diagnostic examination including barium swallow, endoscopy and biopsy, chest radiography, liver function tests and computed tomography. All were given adequate nutritional care and pulmonary physiotherapy, both before and after surgery. At exploration, lesions were considered resectable in only 60 patients. Total oesophagectomy and gastric pull-up to the neck was performed in all patients. Total oesophagectomy was performed by a synchronous three-team approach as described previously[8]. After oesophagectomy and gastric mobilization, patients were randomized by drawing of lots to receive pyloroplasty or not. Pyloroplasty was performed by a standardized Heineke–Mikulicz technique to a length of 6 cm. The stomach was transposed in the mediastinum and oesophagogastrostomy performed to the cervical oesophagus. Of the 60 patients who underwent total oesophagectomy, ten died in the postoperative period and another ten within 6 months of operation. Nine refused to undergo tests for duodenogastric reflux and in seven the study could not be conducted because of technical problems. These included failure to pass a tube beyond the anastomosis, accidental removal of the tube, blood-stained aspirate secondary to traumatic insertion, and persistent retching, which required removal of the nasogastric tube. Thus only 24 patients (12 in each group) were available for this study: 19 men and five women of mean age 49 (range 18–69) years. Nineteen patients had carcinoma and the remaining five extensive corrosive stricture of the oesophagus.

These 24 patients were periodically seen in the follow-up clinic up to 6 months after surgery. During these visits they were carefully interviewed by an independent observer for features believed to be caused by bile reflux, such as postprandial discomfort or fullness, bilious eructations, vomiting, anorexia, anaemia and weight loss.

Patients were also evaluated 6 months after surgery for duodenogastric reflux by estimation of bile acid concentration. A nasogastric tube was placed in the pyloric antrum under radiological control 4 h after a light meal in the evening. Gastric juice was aspirated every hour for 12 h. Total volume and pH of the gastric aspirate were measured in each patient. The samples thus collected were stored at −30°C. The total bile acid concentration in the fasting gastric aspirate was estimated using a standard kit (Sterognost 3 Alpha pho; Nyegard, Oslo, Norway). The intragastric bile acid concentrations were then correlated with symptoms.

Bile acid concentrations were compared using the Wilcoxon rank sum test.

Results

Clinical follow-up

After operation, ten patients experienced postprandial discomfort: six undergoing pyloroplasty and four not. Bilious eructations were observed in 15 patients (seven and eight in the two groups respectively). Similarly, vomiting (three and two patients), anorexia (three and three) and anaemia (six and five) were equally frequent in patients with and without pyloroplasty.

Total bile acid concentration of gastric aspirate

The volume of the aspirate varied considerably, ranging between 300 and 750 ml. Similarly, the pH of the samples varied between 3·5 and 6·8. The mean(s.d.) total bile acid concentration in patients undergoing pyloroplasty was 34·9(30·1) mg/dl and that in those not receiving pyloroplasty 25·0(24·2) mg/dl. The range of bile acid concentration in the two groups was wide, although the majority of patients had values between 10 and 30 mg/dl. No significant difference was demonstrated between the two groups.

When the total bile acid concentration was correlated with postoperative symptoms, no relationship was observed (*Table 1*). Symptoms were present irrespective of the concentration of bile acid and whether or not pyloroplasty had been performed. For example, patient 24 had a high bile acid concentration but no symptoms, whereas patient 23 had a low concentration but several symptoms.

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Table 1 *Gastric juice volume, pH and bile acid content in patients with an intrathoracic stomach with and without pyloroplasty*

Pyloroplasty ($n = 12$)						No pyloroplasty ($n = 12$)					
Patient no.	Symptoms	Volume (ml)	pH	Total bile acid (mg)	Bile acid concentration (mg/dl)	Patient no.	Symptoms	Volume (ml)	pH	Total bile acid (mg)	Bile acid concentration (mg/dl)
2	2, 3, 4, 5	300	3·7	269	89·7	1	2, 4	465	3·5	28	6·0
4	4	345	3·5	31	9·0	3	1, 5	335	3·7	106	31·5
7	1, 2, 3	325	3·5	55	17·0	5	2, 5	420	4·5	70	16·8
8	1, 3, 5	440	5·2	117	26·7	6	1, 2	535	5·0	182	33·9
11	1, 2	480	5·0	233	48·5	9	2, 3, 5	570	5·1	193	33·9
12	0	615	6·3	104	17·0	10	1	520	5·3	95	18·2
17	0	735	6·0	222	30·2	13	0	695	6·5	75	10·8
18	1, 2, 5	385	3·5	74	19·4	14	2	710	6·8	86	12·1
21	1, 2, 5	300	3·5	51	17·0	15	0	485	4·8	112	23·0
22	2, 4, 5	485	5·7	215	44·2	16	2	300	3·5	9	3·0
23	1, 2, 5	685	5·8	42	6·1	19	1, 2, 4, 5	330	4·5	52	15·8
24	0	355	4·0	336	94·6	20	2, 3, 4, 5	750	6·5	709	94·6
Mean(s.d.)		454(151)	4·6(1·1)	146(104)	34·9(30·1)			510(152)	5·0(1·1)	143(186)	25·0(24·2)

Symptoms: 0, none; 1, postprandial fullness or discomfort; 2, bilious eructation; 3, vomiting; 4, anorexia; 5, anaemia

Discussion

Duodenogastric bile reflux is known to occur after various gastric operations including vagotomy. As total oesophagectomy also involves vagotomy, reflux is expected to occur in the vagotomized intrathoracic stomach used for oesophageal replacement. Unfortunately, little is known about this process.

To detect reflux after gastric operations, most authors have used either endoscopy[9] or scintigraphy[10]. These methods are essentially qualitative. Measurement of intragastric bile acid concentration, on the other hand, is a useful quantitative method[11–13]. It records the net concentration of bile acids refluxed into the stomach, which is likely to be related to mucosal changes. Overnight gastric aspiration following a meal takes into account the food-induced bile secretion as well as the dilutional effect of food and gastric juice. We consider estimation of bile acid concentration in an overnight collection of gastric aspirates to be a physiological estimate of gastric mucosal exposure to bile acids.

The postoperative bile acid concentrations in the intrathoracic stomach in the present series were similar 6 months after surgery in patients with and without pyloroplasty. Bile reflux seemed to occur in all patients with an intrathoracic stomach, irrespective of the addition or not of pyloroplasty (*Table 1*).

Mannel *et al.*[14] in a study of patients with an intrathoracic stomach without pyloroplasty reported a mean bile acid concentration of 22·5 mg/dl. They attributed this to increased duodenogastric reflux. Sugiyama *et al.*[15] reported a mean bile acid concentration of 21·2 mg/dl after pylorus-preserving gastrectomy. This surgery, although not identical to oesophagectomy and gastric pull-up, also involves total vagotomy and pyloric denervation, which probably explains the similar results.

Alkaline or biliary gastritis usually presents with a symptom complex of epigastric pain, bile vomiting, anaemia, anorexia and weight loss. These symptoms are reported to be caused by duodenogastric reflux of bile[11,12,16,17].

Hoare *et al.*[11] and Wickremesinghe and colleagues[17] have demonstrated higher bile reflux in symptomatic patients. Svenson[18], on the other hand, believed that, although bile reflux is increased in symptomatic patients, there is no correlation between gastritis and symptoms or gastritis and bile reflux. Bechi *et al.*[19] could not demonstrate a significant difference between histological findings in symptomatic and asymptomatic patients.

In the present study, postprandial discomfort and bilious eructations were the two most common complaints after gastric pull-up operation, occurring equally in patients with or without pyloroplasty. Occasional vomiting, anaemia and anorexia are other features noted in this study, but there was no correlation between bile acid concentration and symptoms in these patients.

In conclusion, this study has demonstrated equal amounts of bile acids in patients with and without pyloroplasty after cervical oesophagogastrostomy. No evidence has been found that the amount of bile reflux is associated with postoperative symptoms in such patients.

References

1. Belsey RHR. Palliative management of esophageal carcinomas. *Am J Surg* 1980; **139**: 789–94.
2. Ong GB, Kwong KH. The Lewis–Tanner operation for cancer of the oesophagus. *J R Coll Surg Edinb* 1969; **14**: 13–19.
3. Wong J. Management of carcinoma of oesophagus – art or science? *J R Coll Surg Edinb* 1981; **26**: 138–49.
4. Angorn IB. Oesophagogastrostomy without a drainage procedure in oesophageal carcinoma. *Br J Surg* 1975; **62**: 601–4.
5. Hinder RA. The effect of posture on the emptying of the intrathoracic vagotomized stomach. *Br J Surg* 1976; **63**: 581–4.
6. Langhans P, Bues M, Bunte H. Morphological changes in operated stomach under the influence of duodenogastric reflux – clinical follow up over 20 years. *Scand J Gastroenterol Suppl* 1984; **92**: 145–8.
7. Mosimann F, Sorgi M, Wolverson RL *et al.* Gastric histology and its relationship to enterogastric reflux after duodenal ulcer surgery. *Scand J Gastroenterol Suppl* 1984; **92**: 142–4.
8. Chattopadhyay TK, Kapoor VK, Sikora SS, Jini M. Synchronous cervical–thoracic–abdominal approach for total oesophagectomy. *Indian J Surg* 1987; **49**: 411–14.
9. Levy N, Stermer E, Boss JM. Accuracy of endoscopy in the diagnosis of inflamed gastric and duodenal mucosa. *Isr J Med Sci* 1985; **21**: 564–8.
10. Muhammed I, McLoughlin GP, Holt S, Taylor TV. Non-invasive estimation of duodenogastric reflux using technetium ^{99m}p-butyl iminodiacetic acid. *Lancet* 1980; **ii**: 1162–5.
11. Hoare AM, Keighley MRB, Starkey B, Alexander Williams J. Measurement of bile acids in fasting gastric aspirates: an objective test for bile reflux after gastric surgery. *Gut* 1978; **19**: 166–9.
12. Ritchie WP. Alkaline reflux gastritis: an objective assessment of its diagnosis and treatment. *Ann Surg* 1980; **192**: 288–98.
13. Watt PCH, Sloan JM, Kennedy TL. Relation between intragastric bile acid concentration and mucosal abnormality in the stomach after vagotomy and enterostomy for duodenal ulcer. *J Clin Pathol* 1984; **37**: 506–10.
14. Mannel A, Hinder RA, San-Garde BA. The thoracic stomach: a study of gastric emptying, bile reflux and mucosal changes. *Br J Surg* 1984; **71**: 438–41.

15. Sugiyama Y, Sohma H, Masanarioza WA *et al.* Regurgitant bile acids and mucosa injury of the gastric remnant after partial gastrectomy. *Am J Surg* 1987; **153**: 399–403.
16. Muller Lissner SA, Fimmel CJ, Sonnenberg A *et al.* A novel approach to quantify reflux in healthy volunteers and in patients with type-I gastric ulcer. *Gut* 1983; **24**: 510–18.
17. Wickremesinghe PC, Dayrit PQ, Manfred OL, Fazio RA, Fagel VL. Quantitative evaluation of bile diversion surgery using ^{99m}Tc-HIDA scintigraphy. *Gastroenterology* 1983; **84**: 354–63.
18. Svenson JO. Duodenal gastric reflux after gastric surgery. *Scand J Gastroenterol* 1983; **6**: 729–34.
19. Bechi P, Amorosi A, Mazzinti R, Romagnoli P, Tonelli L. Gastric histology and fasting bile reflux after partial gastrectomy. *Gastroenterology* 1987; **93**: 335–43.

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Surgical workshop

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Laparoscopic resection of a bleeding gastric tumour

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The successful emergency excision of a bleeding gastric tumour on the greater curve by minimally invasive surgery is reported.

Surgical technique

A 70-year-old man presented with recurrent upper gastrointestinal haemorrhage necessitating multiple blood transfusions. Gastroscopy showed a 2·5-cm elevated ulcerated lesion bleeding high on the anterior wall of the greater curve of the stomach.

Under general anaesthesia, with the patient supine, a laparoscope was inserted through a 10-mm supraumbilical cannula. A 12-mm port was sited on the mid-clavicular line in the left hypogastrium for introduction of a 30-mm Endo-GIA (Auto Suture, Ascot, UK), and a 5-mm cannula was placed in the epigastrium to allow retraction of the liver. Another 10-mm cannula was placed in the lower epigastrium to the right of the falciform ligament for instrument access. A gastroscope was passed into the stomach, and the tumour was located. The gastric wall was raised from the luminal aspect, with a biopsy forceps. The raised area was then grasped with a Babcock's forceps (*Figure 1*).

The greater curve was mobilized, dividing the short gastric vessels with a combination of the Endo-GIA and clip applicators. A cuff of stomach was excised under direct vision, both laparoscopically and gastroscopically, by firing the Endo-GIA sequentially along the mobilized section of the greater curve. The specimen was removed through the supraumbilical cannula. It was opened and inspected to ensure that the resection margins were clear of tumour. The abdominal cavity was inspected for bleeding, and the wounds were closed. The anaesthesia time was 180 min.

The patient tolerated a full diet on the second day after operation and was discharged on the third. Histological examination of the excised specimen showed the lesion to be a metastasis from a renal cell carcinoma removed by nephrectomy in 1980. The excision margins were clear of tumour.

Discussion

Laparoscopic gastric mobilization has been described[1], but the present case demonstrates that it is possible to excise a small gastric tumour laparoscopically with satisfactory resection margins. It would not be possible to locate small gastric lesions accurately by laparoscopy alone; combining the procedure with gastroscopy allows identification of the target lesion and clear definition of the tissue to be resected. This technique is likely to result in lower morbidity and mortality rates than standard open partial gastrectomy, which would ordinarily have been the treatment for this patient.

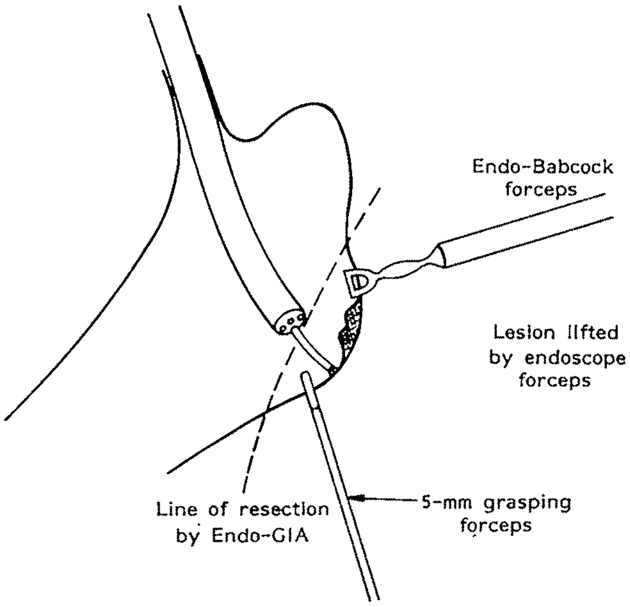
Endo-Babcock forceps
Lesion lifted by endoscope forceps
5-mm grasping forceps
Line of resection by Endo-GIA

Figure 1 *Coronal section through the stomach showing the tumour being raised to allow accurate placement of the laparoscopic grasping instruments*

Sano *et al.*[2] reported a series of patients in whom early gastric carcinoma might be treated by gastroscopic resection. However, their technique precludes pathological assessment of the regional lymph nodes. Laparoscopic gastric resection would allow excision of small gastric tumours with assessment of the regional lymph nodes and the liver, without the risks of open operation.

References

1. Dallemagne B, Weerts JM, Jehaes C *et al.* Case report: subtotal oesophagectomy by thoracoscopy and laparoscopy. *Minimally Invasive Therapy* 1992; **1**: 183–5.
2. Sano T, Kobori O, Muto T. Lymph node metastasis from early gastric cancer: endoscopic resection of tumour. *Br J Surg* 1992; **79**: 241–4.

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374–377

Increasing incidence of carcinoma of the gastric cardia in Sweden from 1970 to 1985

Several American, Japanese and European centres have reported an increase in carcinoma of the gastric cardia, contrary to the general trend in the incidence of gastric cancer. The aim of this nationwide population-based study was to describe trends in the incidence of tumours of the gastric cardia in Sweden over the 16-year period from 1970 to 1985. The Swedish cancer register, which is more than 95 per cent complete, was used to identify cases. There were 1514 men and 481 women with cancer of the gastric cardia. The age-standardized rates increased in men from 1·9 per 10^5 population in 1970–1973 to 3·0 per 10^5 in 1982–1985, corresponding to a mean annual increase of 2·5 per cent (95 per cent confidence interval (c.i.) 1·6–3·4 per cent). In women, the age-standardized rates increased from 0·5 per 10^5 in 1970–1973 to 0·8 per 10^5 in 1982–1985, the mean annual increase being 0·9 per cent (95 per cent c.i. 0·0–1·8 per cent). The highest incidences were found in southern Sweden, contrary to the geographical distribution of gastric cancer in general, which shows a south-to-north gradient. The disparate epidemiological features of cancer of the cardia and gastric cancer at other sites suggest that the aetiologies may also be different. Since little is known about the aetiology of cancer of the cardia, and the incidence seems to be rising rapidly, analytical studies are urgently needed.

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Contrary to the well established downward trend in the incidence of gastric cancer worldwide[1,2], there are several reports of an increase in carcinoma of the gastric cardia, based on hospital series from American[3–7], Japanese[8] and European[9–14] centres. These somewhat unexpected findings have been confirmed by a few population-based studies[15–19]. It remains unclear whether the results reflect a relative increase in relation to stomach cancer at other sites, which has decreased markedly during the past decades, or whether they reflect a genuine upward trend in incidence.

Carcinoma of the cardia has several features that differ from more distally located cancers of the stomach. If it can be convincingly established that the incidence of cancer at the cardia is really increasing, this would strengthen the view that it is a neoplastic entity separate from carcinoma at more distal parts of the stomach.

The aim of this nationwide study was to describe trends in the incidence of tumours of the gastric cardia in Sweden over the 16-year period from 1970 to 1985.

Patients and methods

The Cancer Registry

Nationwide cancer registration started in Sweden in 1958 and since 1970 cancer of the gastric cardia has had its own code number (ICD-8 code 151.01), distinguishing it from stomach cancer at other sites. Physicians are required to report all cases of newly diagnosed cancer to the Cancer Registry at the National Board of Health and Welfare. Pathologists and cytologists must also notify the Registry about every case of cancer that is diagnosed by means of surgically removed tissue, biopsy, cytological specimen or autopsy. In the majority of cases the Registry thus receives two reports; cases identified by death certificates alone are not included in the register. A more extensive description of the Swedish Cancer Registry is given elsewhere[20].

The deficit in the register was estimated in the 1970s to be 4·5 per cent and to be referable mainly to patients older than 75 years and to those with malignant disease of the haematopoietic system[21]. The completeness of the register is now considered to be close to 100 per cent of all diagnosed cases[20].

For this study all subjects in the register identified as having cancer of the gastric cardia in the period from 1970 to 1985 were selected.

Statistical analysis

To avoid the influence of a changing age distribution during the study period, direct standardization was used to calculate age-standardized incidence rates. The Swedish census of 1970 was used as the reference[22]. Time trends for age-standardized rates were estimated by the linear regression model $Y = \mathrm{e}^{\mathrm{a}+\mathrm{b}x}$, where Y is the estimated annual age-standardized incidence per 10^5, x is the calender year minus the mid-point of the period, $\mathrm{a} = (\Sigma \ln y)/n$ and $\mathrm{b} = [\Sigma x(\ln y - \mathrm{a})]/\Sigma x^2$; y is the incidence for each year. This model assumes that the incidence trend during a specific period can be described in terms of a mean annual percentage change[23]. Confidence intervals for b are given for the 95 per cent level according to Student's t distribution with 2 d.f.

Comparisons between geographical regions were made using the method of indirect standardization to calculate the standardized incidence ratio as a measure of relative risk[22]. Confidence intervals at the 95 per cent level were calculated on the assumption that the observed number of cases followed a Poisson distribution.

Results

In a total of 31 148 cases of gastric carcinoma, 1995 patients with cancer of the cardia were found: 1514 men and 481 women. In 1970–1971, 88·5 per cent of the cases were verified by histological analysis; in 1984–1985 this had risen to 97·3 per cent. Some 6·0 per cent were diagnosed radiologically or by other clinical means without histological confirmation in 1970–1971 and 2·1 per cent in 1984–1985. Most of the remaining cases were diagnosed at operation without histological confirmation. In 1970–1971, 2·7 per cent of all cases were first diagnosed at autopsy. The corresponding figures in 1976–1977 and 1984–1985 were 9·1 and 4·8 per cent respectively. The mean annual number of cases diagnosed

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Table 1 *Age-standardized incidence per 10^5 population, sex ratio and number of patients with cancer of the cardia in Sweden from 1970 to 1985, according to age at diagnosis, sex and period of diagnosis*

	Age-standardized incidence												
	1970–1973			1974–1977			1978–1981			1982–1985			1970–1985
	M	F	Sex ratio (M:F)	M	F	Sex ratio (M:F)	M	F	Sex ratio (M:F)	M	F	Sex ratio (M·F)	Sex ratio (M:F)
Age at diagnosis (years)													
<50	0·1 (14)	<0·1 (2)	—	0·1 (9)	<0·1 (6)	—	0·2 (21)	<0·1 (2)	—	0·2 (23)	<0·1 (5)	—	7·0
50–59	1·5 (30)	0·3 (7)	5·0	2·5 (50)	0·6 (12)	4·2	3·4 (65)	0·8 (16)	4·2	3·6 (63)	0·8 (14)	4·5	4·3
60–69	5·1 (87)	1·3 (25)	3·9	6·1 (107)	1·2 (23)	5·1	8·5 (149)	1·8 (34)	4·7	8·6 (150)	2·1 (39)	4·1	4·4
70–79	11·7 (110)	2·4 (28)	4·9	12·6 (127)	3·5 (45)	3·6	10·3 (116)	2·1 (30)	4·9	15·5 (185)	3·6 (55)	4·3	4·4
>80	10·5 (33)	5·0 (24)	2·1	12·0 (41)	6·3 (35)	1·9	15·1 (56)	4·5 (29)	3·4	19·0 (78)	6·6 (50)	2·9	2·6
Total	1·9 (274)	0·5 (86)	3·8	2·2 (334)	0·6 (121)	3·7	2·5 (407)	0·6 (111)	4·2	3·0 (499)	0·8 (163)	3·8	4·1

Values in parentheses are actual numbers of patients

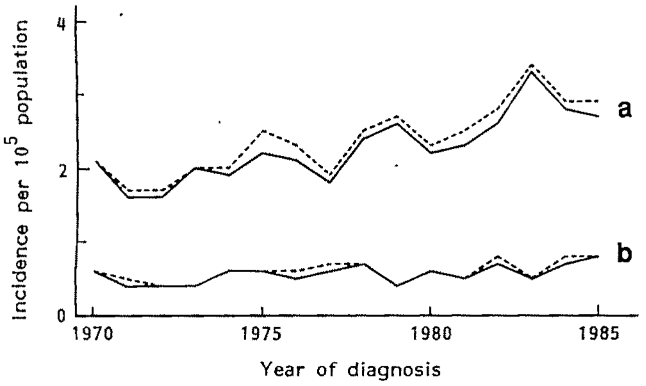

Figure 1 *Age-standardized incidence for cancer of the cardia, including (----) and excluding (——) cases first diagnosed at autopsy, in* **a** *men and* **b** *women in Sweden from 1970 to 1985*

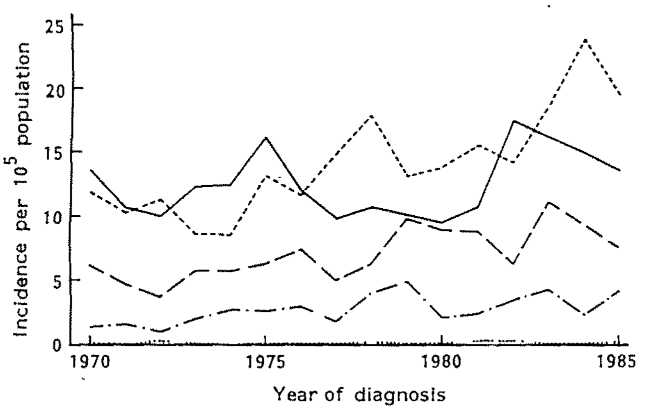

Figure 2 *Age-standardized incidence for cancer of the cardia in men in Sweden from 1970 to 1985 by age. Age: <50 years (·····); 50–59 years (— · —); 60–69 years (——); 70–79 years (——); ≥80 years (----)*

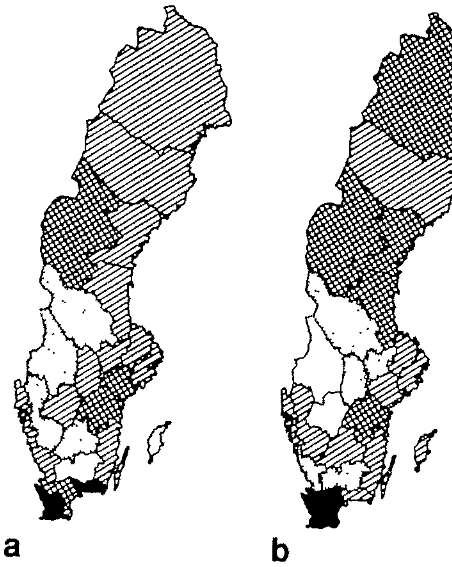

Figure 3 *Relative risk of cancer of the cardia by county for* **a** *men and* **b** *women in Sweden, from 1970 to 1985. Relative risk ratios:* □, *≤0·69;* ▨, *0·70–0·89;* ▨, *0·90–1·09;* ▩, *1·10–1·29;* ■, *≥1·30*

increased from 69 men and 22 women during the first 4-year period to 112 and 41 respectively during the final period. The relative proportion of adenocarcinoma increased from 82·2 per cent in 1970–1971 to 94·6 per cent in 1984–1985. Approximately 2 per cent were squamous cell carcinoma, a percentage that remained unchanged throughout the period. The remaining lesions were unspecified or poorly differentiated tumours. Age-standardized incidences classified by sex and time of diagnosis are shown in *Table 1*. The age-standardized rate increased in men from 1·9 per 10^5 in 1970–1973 to 3·0 per 10^5 in 1982–1985 (58 per cent increase), corresponding to a mean annual increase of 2·5 per cent (95 per cent confidence interval (c.i.) 1·6–3·4 per cent). In women the age-standardized rates increased from 0·5 per 10^5 in 1970–1973 to 0·8 per 10^5 in 1982–1985. This corresponds to a mean annual increase of 0·9 per cent (95 per cent c.i. 0·0–1·8 per cent) (*Figure 1*). The age-specific incidences in men by year of diagnosis are shown in *Figure 2*. The trend was most pronounced in the age groups 50–59 years and ≥80 years, with a mean (95 per cent c.i.) annual increase of 4·3 per cent (1·5–7·1 per cent) and 4·5 per cent (2·5–6·6 per cent) respectively. In women the mean annual increase in the age-specific incidences was 2·3 per cent (95 per cent c.i. 0·6–4·0 per cent) in the 60–69-years age group. In the other age groups the age-specific incidences were stable or showed a slight tendency to increase, without the rise being statistically significant. The male:female ratio (*Table 1*) remained fairly stable at around 4:1 throughout the study period. Since the incidence of stomach cancer was falling[24] in both men and women during the same period there was a marked increase in cancer of the gastric cardia relative to all cases of stomach cancer. The relative percentages of cancer located at the gastric cardia increased in men from 5·1 per cent in 1970–1971 to 11·2 per cent in 1984–1985 and in women from 2·6 to 6·1 per cent.

The relative risk ratios were calculated for each of the 24 counties in Sweden during 1970–1985 (*Figure 3*). The highest ratio was in the county of Malmöhus in the extreme south, at 1·39 (95 per cent c.i. 1·20–1·60) in men and 1·46 (95 per cent c.i. 1·14–1·85) in women. Two counties in central Sweden showed relative risk ratios significantly below unity, the figures for men being 0·75 (95 per cent c.i. 0·58–0·96) and 0·73 (95 per cent c.i. 0·54–0·99) respectively.

Discussion

The main finding in this study is an increase in the age-standardized incidence of carcinoma of the gastric cardia, which was significant in men and less conspicuous in women. This corroborates previous evidence which has suggested that cancer of the gastric cardia may be increasing. Several investigators have found an increasing proportion of proximal gastric cancers in relation to more distal tumours of the stomach[4–6,9,16,20,25]. Since these reports have been based on hospital series, the finding may have reflected selection bias; only population-based studies may answer the question as to whether there is a real increase in incidence. Five such studies have been published hitherto; two British[16,18], one Danish[15] and one American[19] study have indicated that the incidence of cancer of the cardia is rising, both relative to gastric cancer at other sites and, in two studies, in absolute rates. In one small population-based study from the Swiss canton of Vaud[17] no increase in incidence was verified between 1976 and 1987.

The main question in interpreting the present data is whether the increase in incidence is real or merely an effect of improved diagnostic accuracy or a gradual shift in classification. Diagnostic methods have become increasingly sophisticated during the study period. The introduction of fibreoptic endoscopy in clinical practice is reflected in the higher proportion of histologically confirmed cases. Moreover, there is a decreasing proportion of unspecified tumours. If there has been an increasing tendency to classify cancers located in the distal part of the oesophagus as carcinoma of the cardia, this could perhaps explain the apparent rising incidence. However, there are no indications of such a shift in classification; in fact, the incidence of adenocarcinoma of the oesophagus has also been increasing among men, particularly during the 1970s and 1980s (unpublished data). Moreover, the proportion of squamous cell carcinomas among cancers of the cardia was not found to have increased in this study. Another possible explanation is a greater inclination among physicians to use the diagnosis of cancer of the cardia in proximal stomach cancer following the introduction of the special four-digit code for cancer of the cardia in the Swedish cancer register in 1970. However, the difference between the trends over time in men and women contradicts this assumption. Further, if a newly heightened awareness of the diagnosis of cancer of the cardia were the explanation, one might expect a sharp increase in this diagnosis during the first years after its introduction. However, the present findings were quite the opposite: the trend accelerated during the later part of the period under study. A more frequent use of endoscopy might explain the increasing incidence, but the faster increase in male than in female incidence makes this explanation less plausible. Another potential source of artefacts may be a change in the proportion of cases first diagnosed at autopsy. However, this proportion has remained stable, and the trend was the same even when these cases were excluded, as is shown clearly in *Figure 1*.

There seems to be a real increase in the incidence of cancer of the gastric cardia in men. This finding supports the view that the aetiology of tumours of the gastric cardia differs from that of other gastric cancers. The incidence of the latter shows an unequivocal downward trend[16–18].

The age-standardized incidence of cancer of the cardia showed a marked geographical variation (*Figure 3*). Areas with a high incidence lay in the south of Sweden, quite different from the geographical distribution of gastric cancer in general, which is highest in the north of the country[26]. This observation provides additional evidence that carcinoma of the cardia and gastric cancer at other sites may have different aetiologies.

According to Laurén[27], tumours of the intestinal type have previously been found in 57–81 per cent of cases of carcinoma of the cardia, compared with only 48–49 per cent of gastric cancers at other sites[11,28,29]. Cancer of the cardia also seems to be associated with a lower prevalence of atrophic gastritis[3,30,31]. Since the Swedish cancer register does not use Laurén's classification, nor does it contain any information concerning the histology of the gastric mucosa other than the cancer, no conclusions can be drawn from the present study concerning these matters.

The Swedish Cancer Registry does not contain data on previous gastric operations, and so it is not possible to address the question of whether previous gastric surgery is associated with the development of cancer of the cardia. However, preliminary data from an ongoing register-based cohort study of about 7000 patients in Sweden who have undergone vagotomy do not show an increased risk 9–18 years after surgery (A. Ekbom, personal communication).

The male:female ratio in the present study was approximately 4:1. This finding is in line with previous reports of a higher male:female ratio[7,10,15,18,28,32] in carcinoma of the cardia compared with all gastric cancers, which have a male:female ratio[24] of 1·9:1. In this respect cancer of the cardia resembles adenocarcinoma of the oesophagus, the male:female ratio of which is 4·4:1 (unpublished data). The higher male:female ratio in cancer of the cardia has prompted investigators to hypothesize that the impact of smoking and alcohol consumption may be different in cancer of the cardia and gastric tumours at other sites[33]. In an analysis of a clinical series, Kalish *et al.*[30] suggested that there is an association between cancer of the cardia, smoking and alcohol consumption. In three analytical studies of risk factors, cancers of the gastro-oesophageal junction were analysed separately. In a study in the USA[34] the use of alcohol and tobacco and a high consumption of beef and smoked foods were associated with an increased risk of cancer of the cardia, but not of gastric carcinoma at other sites. A Japanese study[35] showed that smoking, but not alcohol consumption, was positively associated with cancer of the cardia. A Chinese study[36] revealed an increased risk associated with smoking and the consumption of wheat and corn, but not of alcohol.

The accumulating evidence that cancer of the cardia is a disease distinct from more distally located gastric cancer implies that future analytical studies of gastric carcinoma should take account of the anatomical location of the tumour. Because little is known about the aetiology of cancer of the cardia, and because its incidence is increasing (at least in the USA and Western Europe) there is a great need for well designed analytical studies of this type of cancer.

References

1. Jensen OM. Trends in the incidence of stomach cancer in the five Nordic countries. In: Magnus K, ed.. *Trends in Cancer Incidence. Causes and Practical Implications.* New York: Hemisphere, 1982: 127–42.
2. Howson CP, Hiyama T, Wynder EL. The decline in gastric cancer: epidemiology of an unplanned triumph. *Epidemiol Rev* 1986; **8**: 1–27.
3. Antonioli DA, Goldman H. Changes in the location and type of gastric adenocarcinoma. *Cancer* 1982; **50**: 775–81.
4. Meyers WC, Damiano RJ, Postlethwait RW, Rotolo FS. Adenocarcinoma of the stomach. Changing patterns over the last 4 decades. *Ann Surg* 1987; **205**: 1–8.
5. Cady B, Choe DS. Changing patterns of gastric cancer. In: Nieburgs ME, ed. *Third International Symposium on Detection and Prevention of Cancer.* New York: Dekker, 1980: 2044–9.
6. Cady B, Rossi RL, Silverman ML, Piccione W, Heck TA. Gastric carcinoma. A disease in transition. *Arch Surg* 1989; **124**: 303–8.
7. Yang PC, Davis S. Epidemiological characteristics of adenocarcinoma of the gastric cardia and distal stomach in the United States 1973–1982. *Int J Epidemiol* 1988; **17**: 293–7.
8. Kampschöer GHM, Nakajima T, van de Velde CJH. Changing patterns in gastric adenocarcinoma. *Br J Surg* 1989; **76**: 914–16.
9. Ottenjann R. Relative Zunahme des Kardiakarzinoms? *Dtsch Med Wochenschr* 1984; **109**: 1303.
10. Sons H, Borchard F. Cancer of the distal oesophagus and cardia. *Ann Surg* 1986; **203**: 188–95.
11. Husemann B. Cardia carcinoma considered as a distinct clinical entity. *Br J Surg* 1989; **76**: 136–9.
12. Paterson IM, Easton DF, Corbishley CM, Gazet J-C. Changing distribution of adenocarcinoma of the stomach. *Br J Surg* 1987; **74**: 481–2.

13. Lund O, Hasenkam JM, Aagaard MT, Kimose HH. Time-related changes in the characteristics of prognostic significance in carcinomas of the oesophagus and cardia. *Br J Surg* 1989; **76**: 1301–7.
14. Golematis B, Tzardis P, Hatzikostas P, Papadimitriou K, Haritopoulos N. Changing pattern of distribution of carcinoma of the stomach. *Br J Surg* 1990; **77**: 63–4.
15. Moller H, Jensen OM. Den tidsmassige udvikling i esophagus-, cardia- og ventrikelcancer i Danmark 1943–1982. *Ugeskr Laeger* 1987; **149**: 1904–9.
16. Allum WH, Powell DJ, McConkey CC, Fielding JWL. Gastric cancer: a 25-year review. *Br J Surg* 1989; **79**: 535–40.
17. Levi F, La Vecchia C, Te V-C. Descriptive epidemiology of adenocarcinomas of the cardia and distal stomach in the Swiss canton of Vaud. *Tumori* 1990; **76**: 167–71.
18. Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. *Br J Cancer* 1990; **62**: 440–3.
19. Blot WJ, Devesa SS, Kneller RW, Fraumeni JF Jr. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA* 1991; **265**: 1287–9.
20. The Cancer Registry. *Cancer Incidence in Sweden 1984.* Stockholm: National Board of Health of Welfare, 1987.
21. Mattsson B, Wallgren A. Completeness of the Swedish Cancer Register. Non-notified cancer cases recorded on death certificates in 1978. *Acta Radiol* (*Oncol*) 1984; **23**: 305–15.
22. Fleiss JL. The standardization of rates. In: *Statistical Methods for Rates and Proportions.* New York: J Wiley, 1981: 270–1.
23. Kleinbaum DG, Kupper LL, Muller KE. *Applied Regression Analysis and Other Multivariable Methods.* 2nd ed. Boston: Kent, 1988.
24. Hansson L-E, Bergstrom R, Sparén P, Adami H-O. The decline in the incidence of stomach cancer in Sweden 1960–1984: a birth cohort phenomenon. *Int J Cancer* 1991; **47**: 499–503.
25. Wang HH, Antonioli DA, Goldman H. Comparative features of esophageal and gastric adenocarcinomas: recent changes in type and frequency. *Hum Pathol* 1986; **17**: 482–7.
26. Moller Jensen O, Carstensen B, Glattre E, Malker B, Pukkala E, Tulinius H. *Atlas of Cancer Incidence in the Nordic Countries.* Helsinki: Nordic Cancer Union, 1988.
27. Laurén P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal type carcinoma. *Acta Pathol Microbiol Scand* 1965; **64**: 31–49.
28. Heidl G, Awlasewicz S, Dunkel K, Langhans P. Das Kardiakarzinom als eigenständige Entität des Magenkarzinoms. In: Langhans P, Schreiber HW, Häring R *et al.*, eds. *Aktuelle Therapie des Kardiakarzinoms.* Berlin: Springer-Verlag, 1988: 29–33.
29. Sidoni A, Lancia D, Pietropaoli N, Ferri I. Changing patterns in gastric carcinoma. *Tumori* 1989; **75**: 605–8.
30. Kalish RJ, Clancy PE, Orringer MB, Appelmann HD. Clinical, epidemiologic, and morphologic comparison between adenocarcinomas arising in Barrett's esophageal mucosa and in the gastric cardia. *Gastroenterology* 1984; **86**: 461–7.
31. MacDonald WC. Clinical and pathologic features of adenocarcinoma of the gastric cardia. *Cancer* 1972; **29**: 724–32.
32. MacDonald WC, MacDonald JB. Adenocarcinoma of the esophagus and/or gastric cardia. *Cancer* 1987; **60**: 1094–8.
33. Flamant R, Lasserre P, Lazar P, Lequerinais J, Denois P, Schwartz D. Differences in sex ratio according to cancer site and possible relationship with use of tobacco and alcohol. Review of 65 000 cases. *J Natl Cancer Inst* 1964; **32**: 1309–16.
34. Wu-Williams AH, Yu MC, Mack TM. Life-style, workplace, and stomach cancer by subsite in young men of Los Angeles county. *Cancer Res* 1990; **50**: 2569–76.
35. Unakami M, Hara M, Fukuchi S, Akiyama H. Cancer of the gastric cardia and the habit of smoking. *Acta Pathol Jpn* 1989; **39**: 420–4.
36. Li J-Y, Ershow AG, Chen Z-J, Wacholder S *et al.* A case–control study of cancer of the esophagus and gastric cardia in Linxian. *Int J Cancer* 1989; **43**: 755–61.

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Gastric cancer and *Helicobacter pylori* infection

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Gastric adenocarcinoma can be divided into two histopathological types: intestinal and diffuse. In addition to the role of environmental factors, an association between gastric cancer and Helicobacter pylori *has been suggested. A retrospective study was therefore carried out among 46 patients who had gastric cancer. As a control group, 40 patients with non-malignant disorders were selected (11 patients with peptic ulcer, 12 with chronic superficial gastritis, 17 with chronic atrophic gastritis). Twenty-six cancers were classified as intestinal type and 20 as diffuse type.* H. pylori *was found in 23 (88 per cent) of the intestinal type and 11 (55 per cent) of the diffuse type* ($P < 0.05$)*. Patients with the intestinal-type gastric cancer had a higher prevalence of* H. pylori *infection than those with gastric ulcer (55 per cent) and chronic superficial gastritis (50 per cent)* ($P < 0.05$)*. These findings suggest that there is a possible association between the intestinal type of gastric cancer and* H. pylori *infection.*

Gastric cancer is one of the most important causes of death from malignant diseases, and has considerable geographical variation in incidence. According to epidemiological studies, the intestinal type of gastric carcinoma is common in high-risk areas[1,2]. It is believed that environmental and socioeconomic factors play an important role in the pathogenesis of the intestinal type of gastric cancer. In the diffuse type, genetic factors and race are thought to be more important.

The significance of chronic gastritis and intestinal metaplasia in the development of gastric carcinoma has been assessed[3–5], but there have been few studies of the association between *Helicobacter pylori* and gastric cancer[6–10]. However, epidemiological studies have shown that *H. pylori* has a high prevalence in certain areas of China and some other parts of the world where gastric cancer is common[11–14].

The aim of this study was to determine the presence of *H. pylori* infection in patients with gastric cancer and to investigate the relationship between *H. pylori* infection and the two types of gastric adenocarcinoma.

Patients and methods

Forty-six consecutive patients from different parts of Turkey were studied who had undergone gastrectomy for gastric cancer in the Oncology Hospital, Ankara, between 1986 and 1991. There were 32 men and 14 women; the mean age was 55 (range 31–80) years. Forty subjects without gastric cancer were studied as a control group; these comprised 27 men and 13 women of mean age 54 (range 27–75) years.

Haematoxylin and eosin stained slides of gastrectomy specimens from the patients with cancer and endoscopic biopsy material from the control group were re-evaluated. The tumours were classified according to Laurén into two types: intestinal and diffuse[15]. Two new slides were prepared for each patient from the uninvaded tissue surrounding the tumour. These were observed under 1000 × immersion magnification after staining with haematoxylin and eosin to identify *H. pylori*. The slides in which *H. pylori* were not detected were restained with Giemsa stain and re-evaluated for the presence of bacteria.

χ^2 and Fisher's exact test were used for statistical analysis. $P < 0.05$ was considered significant.

Results

Twenty-six cancers were classified as intestinal type and 20 as diffuse type. Tumour localization of the patients according to histological type and biopsy site of the control subjects is shown in *Table 1*.

H. pylori was present in 34 (74 per cent) of the patients, in 23 (88 per cent) with intestinal-type and 11 (55 per cent) with diffuse-type gastric adenocarcinoma. This difference was statistically significant ($P < 0.05$). *H. pylori* was present in 24 (60 per cent) of the control subjects (*Table 2*). Patients with the intestinal type of gastric cancer had a higher rate of *H. pylori* infection than those with gastric ulcer and chronic superficial gastritis ($P < 0.05$). The difference between the prevalence rate of *H. pylori* in chronic atrophic gastritis and intestinal-type cancer was not statistically significant.

Table 1 *Distribution of tumour localization according to histological type, and biopsy site of the control subjects*

	Antrum	Fundus	Cardia	Total
Gastric cancer type				
Intestinal	18 (69)	5 (19)	3 (12)	26
Diffuse	9 (45)	8 (40)	3 (15)	20
Controls	19 (48)	13 (32)	8 (20)	40

Values in parentheses are percentages

Table 2 *Presence of* Helicobacter pylori *related to the histological type of gastric cancer and diagnosis in the control group*

	H. pylori-positive cases
Gastric cancer type	
Intestinal	23 of 26 (88)
Diffuse	11 of 20 (55)*
Controls	
Peptic ulcer	6 of 11 (55)*
Chronic superficial gastritis	6 of 12 (50)*
Chronic atrophic gastritis	12 of 17 (71)

Values in parentheses are percentages. * $P < 0.05$ *versus* intestinal-type gastric cancer (Fisher's exact test)

Discussion

The prevalence of *H. pylori* infection in the normal population is 50 per cent[16,17]. Although there are many studies concerning the effect of *H. pylori* infection on peptic ulcer and gastritis, there are limited published data relating to *H. pylori* and gastric cancer[18–23]. The present study demonstrates an association between infection with this bacterium and intestinal-type gastric

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cancer. In diffuse-type cancer the *H. pylori* infection rate was similar to that seen in peptic ulcer and chronic superficial gastritis in the control group. Similar results were obtained recently by Parsonnet *et al.*[10].

It is clear that, in the aetiology of the intestinal type of gastric cancer, high-risk areas and environmental factors play an important role. *H. pylori* infection may be a cofactor in the development of gastric cancer, especially of the intestinal type, as there is a well known direct relationship between *H. pylori* infection and chronic gastritis, which is a premalignant lesion.

Bacterial infection may cause cancer by several mechanisms. *H. pylori* has urease activity that produces ammonia from urea secreted by the mucosa into the lumen[17]. Ammonia can damage the Na^+–K^+ ATPase pump by displacing adenosine 5′-triphosphate (ATP) and causing back diffusion of H^+ ions. Because of this back diffusion, hypochloric hypoacidity occurs, and cell necrosis and inflammation result from the high intracellular H^+ ion concentration. During long periods of inflammation an increase in the secretion of endogenous and exogenous mutagens will cause DNA damage[24].

These findings indicate that *H. pylori* infection may be a cofactor in the development of the intestinal-type gastric cancer. It is possible that treatment of *H. pylori* infection might play a role in the prevention of gastric adenocarcinoma.

References

1. Munoz N, Connelly R. Time trends of intestinal and diffuse types of gastric cancer in the United States. *Int J Cancer* 1971; **8**: 158–64.
2. Munoz N, Correa P, Cuello C, Duque E. Histologic types of gastric carcinoma in high- and low-risk areas. *Int J Cancer* 1968; 3: 809–18.
3. Correa P, Cuello C, Duque E *et al.* Gastric cancer in Colombia. III. Natural history of precursor lesions. *J Natl Cancer Inst* 1976; **57**: 1027–33.
4. Correa P. A human model of gastric carcinogenesis. *Cancer Res* 1988; **48**: 3554–60.
5. Sipponen P, Kosunen TU, Valle J, Riihela M, Seppala K. *Helicobacter pylori* infection and chronic gastritis in gastric cancer. *J Clin Pathol* 1992; **45**: 319–23.
6. Correa P, Ruiz B, Taylor N, Portilla H. *Helicobacter pylori* and gastric carcinoma. *Cancer* 1990; **66**: 2569–74.
7. Feng Y, Wang Y. *Campylobacter pylori* in patients with gastritis, peptic ulcer, and carcinoma of the stomach in Lanzhou, China. *Lancet* 1988; i: 1055–6.
8. Jiang SJ, Lui WZ, Zhang DZ *et al.* Campylobacter-like organisms in chronic gastritis, peptic ulcer, and gastric carcinoma. *Scand J Gastroenterol* 1987; **22**: 553–8.
9. Loffeld RJLF, Willems I, Flendring JA, Arends JW. *Helicobacter pylori* and gastric carcinoma. *Histopathology* 1990; **17**: 537–41.
10. Parsonnet J, Vandersteen D, Goates J, Sibley RK, Piritikin J, Chang Y. *Helicobacter pylori* infection on intestinal- and diffuse-type gastric adenocarcinomas. *J Natl Cancer Inst* 1991; **83**: 640–3.
11. Forman D, Sitas F, Newell DG *et al.* Geographic association of *Helicobacter pylori* antibody prevalence and gastric cancer mortality in rural China. *Int J Cancer* 1990; **46**: 608–11.
12. Burstein M, Monge E, Leon-Barua R *et al.* Low peptic ulcer and high gastric cancer prevalence in a developing country with a high prevalence of infection by *Helicobacter pylori. J Clin Gastroenterol* 1991; **13**: 154–6.
13. Forman D, Newell DG, Fullerton F *et al.* Association between infection with *Helicobacter pylori* and risk of gastric cancer: evidence from a prospective investigation. *BMJ* 1991; **302**: 1302–5.
14. Parsonnet J, Friedman GD, Vandersteen DP *et al. Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 1991; **325**: 1127–31.
15. Laurén P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. *Acta Pathol Microbiol Scand* 1965; **64**: 31–49.
16. Schubert TT, Schnell GA. Prevalence of *Campylobacter pylori* in patients undergoing upper endoscopy. *Am J Gastroenterol* 1989; **84**: 637–42.
17. Chamberlain MCE, Peura CDA. *Campylobacter* (*Helicobacter*) *pylori*: is peptic disease a bacterial infection? *Arch Intern Med* 1990; **150**: 951–5.
18. Blaser MJ. Gastric campylobacter-like organisms, gastritis, and peptic ulcer disease. *Gastroenterology* 1987; **93**: 371–83.
19. Booth L, Holdstock G, MacBride H *et al.* Clinical importance of campylobacter pyloritis and associated serum IgG and IgA antibody responses in patients undergoing upper gastrointestinal endoscopy. *J Clin Pathol* 1986; **39**: 215–19.
20. Caruso ML, Fucci L. Histological identification of *Helicobacter pylori* in early and advanced gastric cancer. *J Clin Gastroenterol* 1990; **12**: 601–2.
21. Goodwin CS, Blincow E, Peterson G *et al.* Enzyme-linked immunosorbent assay for campylobacter pyloritis: correlation with presence of *C. pylori* in the gastric mucosa. *J Infect Dis* 1987; **155**: 488–94.
22. Price AB, Levi J, Dolby JM *et al.* Campylobacter pyloritis in peptic ulcer disease: microbiology, pathology, and scanning electron microscopy. *Gut* 1985; **26**: 1183–8.
23. Warren JR, Marshall B. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; i: 1273–5.
24. Ames BN, Gold LS. Too many rodent carcinogens: mitogenesis increases mutagenesis. *Science* 1990; **249**: 970–1.

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Resection of presumed benign liver tumours

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The surgical treatment of benign liver tumours (focal nodular hyperplasia (FNH) and hepatic adenoma) remains controversial. From 1984 to 1990, all 51 women aged below 50 years who presented with presumed benign liver tumours and without chronic liver disease underwent tumour resection. Preoperative assessment included liver tests, ultrasonography and dynamic computed tomography in all patients, plus angiography ($n = 20$), *magnetic resonance imaging* ($n = 22$) *and technetium–sulphur colloid liver scintigraphy* ($n = 19$). *The aims of this study were to compare preoperative and final pathological diagnosis and determine whether surgical treatment was justified. Preoperative assessment suggested FNH in 18 patients and hepatic adenoma in 11. In 22 patients, the distinction between FNH and adenoma could not be determined before operation. Operative procedures included resection of one segment or less in 22 patients, two segments in 14 and three or more segments in 15. There was no postoperative death and no serious complication. The final diagnosis after pathological examination of resected specimens was FNH in 36 patients (71 per cent), including the 18 presumed before operation to have FNH, hepatic adenoma in 12 (24 per cent) and malignant lesions in three (6 per cent): hepatocellular carcinoma (HCC) arising in normal liver, fibrolamellar carcinoma, and adenoma containing areas of HCC in one patient each. In conclusion: (1) precise preoperative diagnosis of benign liver tumours remains difficult despite new imaging methods; (2) malignant liver tumours can go unrecognized; and (3) resection of all these lesions can be carried out safely. Resection of presumed benign liver tumours should be performed in young women when a preoperative diagnosis of FNH is not firmly established.*

Benign liver tumours, including focal nodular hyperplasia (FNH) and hepatic adenoma, are uncommon and most often affect young women[1]. Bleeding, tumour necrosis and neoplastic degeneration have been reported in hepatic adenoma[2–6]; resection is therefore advocated[7,8]. In contrast, FNH may be treated conservatively because it is often an incidental finding and there is no convincing report showing that these tumours can bleed or degenerate[1,7]. Percutaneous needle biopsy cannot distinguish hepatic adenoma from FNH with accuracy[7,9]. Although combined use of scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI) and angiography can aid the therapeutic decision, the differentiation between these two tumours before surgery remains difficult[10,11].

From 1984, all young women referred to this hospital for presumed benign liver tumours were prospectively assessed by imaging procedures and underwent hepatic resection. The aims of this study were twofold: to compare preoperative and final pathological diagnosis and to establish whether surgical treatment of these tumours is justified.

Patients and methods

From March 1984 to December 1990, all women aged <50 years with presumed benign liver tumours (i.e. FNH or hepatic adenoma) underwent radical tumour resection. Fifty-one women having all the following characteristics were included in this study: (1) absence of chronic liver disease; (2) normal serum α-fetoprotein level; (3) one to three tumours detected by ultrasonography; (4) an early marked and transient opacification of the tumour observed on CT during the venous phase; and (5) no invasion of vessels demonstrated by imaging methods.

The mean(s.d.) age of patients was 32(7) (range 18–48) years; 38 (75 per cent) had a history of oral contraceptive use for a mean(s.d.) of 8(5) (range 1–20) years. Thirty-two women (63 per cent) complained of abdominal pain which was acute in six; two (4 per cent) had a palpable mass and 17 (33 per cent) were clinically asymptomatic. Asymptomatic tumours were discovered by ultrasonography in 15 cases and incidentally at laparotomy in two.

Laboratory analyses including haemoglobin and fibrinogen levels, platelet count and liver tests (alkaline phosphatase, aminotransferases, bilirubin, γ-glutamyl transpeptidase (GGT)) were performed before operation in all patients and were normal in 21 (41 per cent). Fibrinogen level was >400 mg/dl in 20 patients (39 per cent), while liver test results were abnormal in 25 (49 per cent).

In addition to ultrasonography (UM 9; Advanced Technology Laboratories, Washington, USA) and CT (DRG 1; Siemens, Erlangen, Germany), performed routinely in all patients, MRI (2T Gyrex; Elscint, Haïfa, Israel), angiography and technetium–sulphur colloid liver scintigraphy (Gammatome II; Sophamédical, Buc-sur-Yvette, France) were performed in 22, 20 and 19 patients respectively. After these investigations, all patients were assessed and the tumour was classified using predefined criteria as either FNH, hepatic adenoma or undetermined between the two. A diagnosis of FNH was suspected if all the following imaging criteria were present: (1) homogeneous hypervascularized mass with a central scar on CT[12]; (2) homogeneous mass isodense with adjacent liver and a hyperdense central scar on T2-weighted sequences at MRI[13] (*Figure 1*); (3) a central feeding artery on angiography or CT[12]; and (4) a normal or increased uptake on technetium–sulphur colloid liver scintigraphy. Hepatic adenoma was suspected if there was intratumour haemorrhage or necrosis on CT or MRI (*Figure 2*). The presumed preoperative diagnosis was FNH in 18 patients and adenoma in 11. In 22 patients no distinction between FNH or adenoma could be made.

Surgical procedures included intraoperative ultrasonography to determine the size and location of the tumour as well as the relationship between the lesion and the vascular system. In all cases, resection was carried out with temporary hepatic inflow occlusion. Resection

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consisted of segmentectomy or enucleation in 22 patients, bisegmentectomy in 14 and trisegmentectomy or more in 15.

Postoperative complications and results of liver tests 3 months after resection were noted. Pathological examination criteria of the resected specimen included final diagnosis, tumour size and the presence of necrotic areas within the lesion. Hepatic adenoma was defined as a tumour consisting of liver cells only, arranged in plates two or three cells thick, and separated by compressed or dilated sinusoids. FNH was defined as a lesion composed of nodules of hepatocytes of normal appearance separated by fibrous septa containing abnormal vessels, proliferating bile ducts and chronic inflammatory cells[9,14].

Student's t test and χ^2 analysis with Yates' correction were used for statistical analysis. Significance was defined as $P < 0{\cdot}05$.

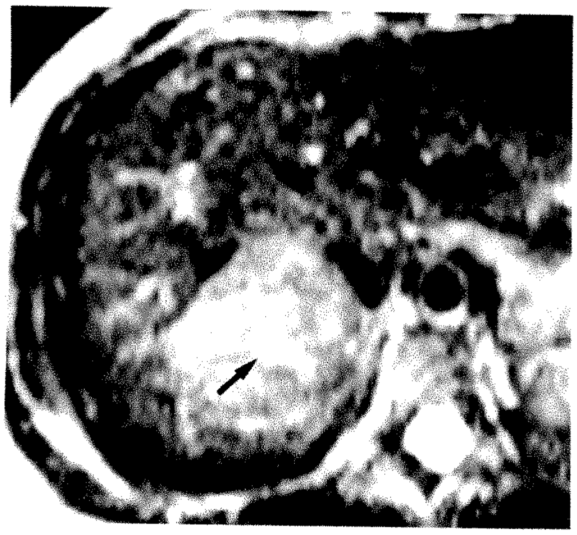

Figure 1 *Focal nodular hyperplasia: T2-weighted axial magnetic resonance image showing mildly increased signal intensity of the lesion. Note the greatly increased signal intensity of the scar (arrow)*

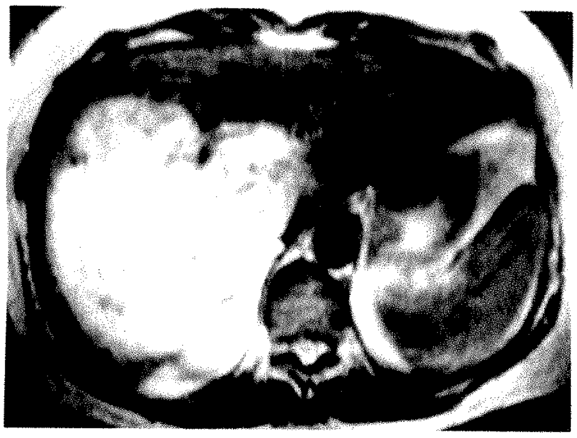

Figure 2 *Hepatic adenoma: T2-weighted axial magnetic resonance image showing extremely heterogeneous increased signal intensity of the lesion*

Results

Comparison between preoperative and postoperative diagnosis

The final diagnosis was FNH in 36 patients (71 per cent), hepatic adenoma in 12 (24 per cent) and malignancy in three (6 per cent), including one hepatocellular carcinoma (HCC) arising in a normal liver, one fibrolamellar carcinoma and one adenoma containing areas of carcinoma. As shown in *Table 1*, all preoperative diagnoses of FNH were confirmed after surgery; of the 11 patients with a preoperative diagnosis of hepatic adenoma, nine had adenoma, two had malignant liver tumours and none had FNH. In the group in whom the diagnosis was undetermined between FNH and hepatic adenoma, 18 had FNH, three adenoma and one a fibrolamellar carcinoma.

Patient characteristics

The three patients with malignant lesions were aged from 23 to 25 years; all had used oral contraceptives for 2–6 years. All three complained of abdominal pain. The fibrinogen level was >400 mg/dl in all cases. Liver test results were normal in the patient with fibrolamellar carcinoma. In the two other patients with HCC, increased alkaline phosphatase and GGT levels were observed.

Clinical and biochemical findings in the 48 patients with proven benign liver tumours are shown in *Table 2*. The prevalence of oral contraceptive use was higher in hepatic adenoma than FNH but the difference was not statistically significant. Abdominal pain was observed in 92 per cent of patients with adenoma and 50 per cent of those with FNH ($P < 0{\cdot}05$). Acute abdominal pain, observed in six patients with hepatic adenoma, could have been related to haemorrhage within the tumour as confirmed by pathological examination.

Table 2 *Clinical, biochemical and gross pathological features in 48 patients with histologically proven benign liver tumours*

	Focal nodular hyperplasia ($n = 36$)	Hepatic adenoma ($n = 12$)
Mean (range) age (years)	32 (17–48)	33 (25–42)
Oral conceptive use*	24 (67)	11 (92)
Symptoms*		
None	16 (44)	1 (8)
Abdominal pain	18 (50)	11 (92)§
Palpable abdominal mass	2 (6)	0 (0)
Biochemical findings*		
Fibrinogen >400 mg/dl	6 (17)	8 (67)‡
Aminotransferases >40 units/l	2 (6)	2 (17)
γ-glutamyl transpeptidase >70 units/l	7 (19)	9 (75)‡
Alkaline phosphatase >120 units/l	0 (0)	7 (58)†
Pathological findings		
Single tumour*	31 (86)	11 (92)
Mean(s.d.) tumour size (cm)	6·4(3·8)	9·2(3·4)§

*Values in parentheses are percentages. †$P < 0{\cdot}001$; ‡$P < 0{\cdot}01$; §$P < 0{\cdot}05$

Table 1 *Preoperative and final pathological diagnosis in 51 patients with presumed benign liver tumours*

	Preoperative diagnosis	Pathological diagnosis		
		Focal nodular hyperplasia	Hepatic adenoma	Hepatic carcinoma
Focal nodular hyperplasia	18	18 (100)	0	0
Hepatic adenoma	11	0	9 (82)	2*
Undetermined benign liver tumour	22	18	3	1†

Values in parentheses are percentage of patients where the presumed diagnosis was confirmed by pathological examination. *One hepatocellular carcinoma (HCC), one lesion with areas of HCC inside an adenoma; †fibrolamellar carcinoma

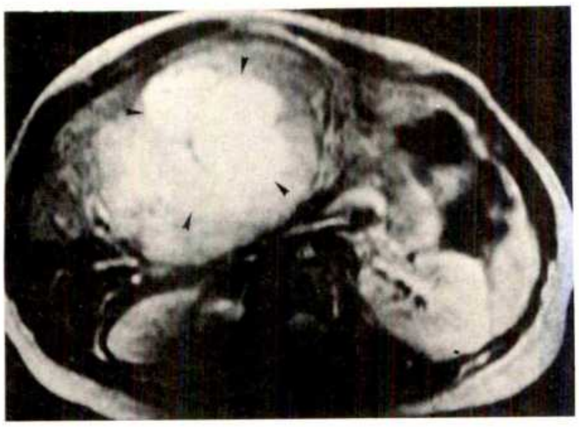

Figure 3 *Non-fibrolamellar hepatocellular carcinoma: T2-weighted axial magnetic resonance image showing a heterogeneous lesion with a central hyperdense area of necrosis (arrows)*

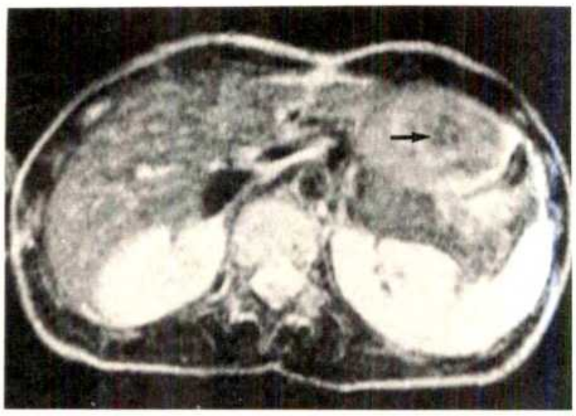

Figure 4 *Fibrolamellar carcinoma: T2-weighted axial magnetic resonance image demonstrating a well circumscribed lesion of the left lobe. The central area is hypodense and corresponds to fibrosis (arrow)*

A fibrinogen level >400 mg/dl was observed in eight patients with adenoma and six with FNH ($P < 0{\cdot}01$). Liver test results were abnormal in ten patients with hepatic adenoma (83 per cent) and eight with FNH (22 per cent) ($P < 0{\cdot}001$). A GGT level >70 units/l was the most frequent abnormality observed. The alkaline phosphatase level was >120 units/l in seven patients with hepatic adenoma but in none with FNH ($P < 0{\cdot}001$).

Pathological findings

The examination of non-involved liver showed the absence of chronic disease in all cases. Tumours were located in the right lobe in 36 patients (71 per cent). Six patients (12 per cent) had more than one tumour: two had two FNH lesions, three had three such tumours and one had three adenomas. The diameter of the tumours ranged from 2 to 18 (mean(s.d.) 7·5(3·7)) cm. The mean diameter for hepatic adenoma was significantly greater than for FNH ($P < 0{\cdot}05$). Intratumour haemorrhage was noted in six cases of adenoma.

All 36 cases of FNH and 12 of adenoma were unequivocally benign. One malignant tumour was a typical fibrolamellar carcinoma with characteristic fibrous stroma and eosinophilic tumour cells. One tumour was a moderately well differentiated trabecular HCC. The macroscopic appearance of the third non-benign tumour strongly suggested malignancy, with a large heterogeneous tumour surrounded by small nodules. The main tumour consisted predominantly of regular and thin hepatocellular plates with no atypia, consistent with adenoma. However, some areas in the main tumour together with the small nodules showed severe atypia with thickened plates, acinar arrangement and nuclear pleomorphism. The tumour was diagnosed as hepatic adenoma with areas of well differentiated trabecular HCC, although no vascular invasion was seen.

Imaging techniques

Of the 36 patients with FNH, 18 had all the predefined imaging criteria described above. In the 18 other cases of FNH, unclassified before surgery, the following features were noted: heterogeneous tumour in ten of 18; absence of central scar in 14 of 18; absence of a central artery at angiography or CT in eight of 12; and isotope defect on technetium–sulphur colloid scintigraphy in 11 of 15. Of the 12 cases of hepatic adenoma, three patients with homogeneous tumours were not diagnosed before operation. For the three patients with malignant tumours, two with heterogeneous tumour with haemorrhage were clinically diagnosed as adenoma (*Figure 3*); the patient with fibrolamellar carcinoma, unclassified before surgery, had a central scar on MRI (*Figure 4*), corresponding to areas of fibrotic tissue in the resected specimen.

Operative results

There were no postoperative deaths. Minor complications occurred in six patients (12 per cent) including pleural effusion in three and an intra-abdominal fluid collection in three, all treated conservatively. The mean(s.d.) hospital stay was 13(4) (range 8–21) days. On follow-up, ranging from 6 to 72 (mean 26) months, all patients are alive with no evidence of tumour recurrence.

Discussion

Correct analysis of reported series on the presentation and diagnosis of hepatic adenoma and FNH is difficult because preoperative evaluation is often incomplete and the pathological diagnosis often poorly documented in unoperated patients[15]. In contrast, the present prospective study with complete pathological analysis of the specimen documented precise clinical, biological and imaging features of both adenoma and FNH. Accurate distinction between adenoma, FNH and malignant tumour before surgery remains difficult. A malignant lesion was found in three of the present patients (6 per cent).

Hepatic adenoma and FNH are uncommon tumours, affecting primarily young women[1]. In the present series, oral contraceptive use was less common in women with FNH than in those with adenoma (67 *versus* 92 per cent). Such data confirm the strong association between oral contraceptives and hepatic adenoma[1,16]. FNH observed in women taking oral contraceptives reflects the high rate of young women taking such contraceptives in western countries. Clinical presentation is different for FNH and adenoma[8,17]. In the present series, FNH was often an incidental finding (44 per cent of cases), while women with adenoma had a higher prevalence of symptoms, probably caused by the greater size of the lesion and the 50 per cent rate of intratumour haemorrhage.

Abnormal liver test results and a high fibrinogen level were observed more frequently in the present patients with hepatic adenoma. Biochemical changes observed in adenoma may be explained by the greater size of the lesion and by intratumour haemorrhage. A rise in alkaline phosphatase level was observed in the present series only in patients with adenoma or malignant tumours and in no case of FNH. Thus, the authors advise against a conservative approach in presumed benign liver tumours associated with these biochemical abnormalities.

Advances in imaging techniques might improve preoperative diagnosis. Ultrasonography is non-specific for tumour differentiation, as all echostructural patterns can be observed in both FNH and adenoma[10]. CT permits an accurate diagnosis in typical cases, showing a homogeneous enhancement with a central scar in FNH and a hyperdense mass with heterogeneous enhancement in adenoma[12,18]. However, as observed in other studies, typical features on CT were found in only 50 per cent of patients with FNH and 75 per cent of those with hepatic adenoma[12]. This study confirms the accuracy of MRI for FNH in half of the cases when there is a homogeneous signal intensity on T1- and a hyperintense central scar on T2-weighted sequences[11,19]. In the case of hepatic adenoma with haemorrhage, MRI shows the signal characteristics of blood[20]. Finally, as shown by the results of this study, differentiation between adenoma and malignant lesions remains difficult with imaging procedures. At angiography, only one-third of FNH lesions had the typical central artery. On technetium–sulphur colloid liver scintigraphy, all patients with normal uptake had FNH. However, recent data demonstrate the lack of specificity of liver scintigraphy, with normal uptake also observed in one-quarter of hepatic adenomas[21].

Percutaneous ultrasonographically or CT-guided liver biopsy is recommended by some authors[17]. In the present study, preoperative biopsy was not performed because the interpretation of the biopsy specimen is hard in the presence of intratumour haemorrhage, the differentiation between adenoma and well differentiated HCC remains difficult, and the risk of bleeding in these hypervascular tumours is high[7].

This study demonstrates that with accurate imaging techniques 50 per cent of cases of FNH can be correctly diagnosed before operation. There is no evidence that FNH lesions can bleed or undergo malignant transformation[1,17]. Thus, management of this condition requires a flexible approach: patients with asymptomatic lesions can be monitored with repeated ultrasonography and undergo resection only if symptoms appear and/or if the tumour enlarges. Although a few cases of regression of hepatic adenoma after discontinuation of oral contraception have been reported[22,23], the authors advocate excision of all presumed adenomas irrespective of signs and symptoms because conservative treatment could lead to overlooking a malignant tumour, as in one patient in the present series, and because malignant transformation of hepatic adenoma has been reported[1,4,6,24]. The high incidence of intratumour haemorrhage, which was observed in 50 per cent of the present cases, and the risk of intraperitoneal rupture are further arguments for resection[8]. In the patients in this series with undetermined tumours, final results after resection indicated FNH in 82 per cent of cases, reflecting the higher prevalence of this tumour. However, in the other patients with undetermined tumours presumed benign, not only was hepatic adenoma found, but also fibrolamellar carcinoma. This tumour affects young patients without underlying liver disease and with normal α-fetoprotein levels[25]. The clinical and biochemical characteristics of fibrolamellar carcinoma are non-specific but the radiating appearances of tumour on imaging can mimic FNH[11]. Thus, all patients with undetermined presumed benign liver lesions should be operated on and are best treated by surgical excision. In some cases, should the location of the tumour make resection hazardous, a large surgical biopsy can be performed to avoid the risk of resection for FNH.

In conclusion, when preoperative diagnosis of FNH in young women cannot be firmly established, surgical excision of presumed benign liver tumours is recommended. This can be done safely in a specialized surgical unit.

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References

1. Kerlin P, Davis GL, McGill DB, Weiland LH, Adson MA, Sheedy PF. Hepatic adenoma and focal nodular hyperplasia: clinical, pathologic and radiologic features. *Gastroenterology* 1983; **84**: 994–1002.
2. Adson MA, Weiland LH. Resection of primary solid hepatic tumors. *Am J Surg* 1981; **141**: 18–21.
3. Ameriks JA, Thompson NW, Frey CF. Hepatic cell adenomas, spontaneous liver rupture and oral contraceptives. *Arch Surg* 1975; **110**: 548–57.
4. Davis M, Postmann B, Searle M, Wright R, Williams R. Histologic evidence of carcinoma in a hepatic tumour associated with oral contraceptives. *BMJ* 1975; **ii**: 496–8.
5. Klastin G. Hepatic tumors: possible relationship to use of oral contraceptives. *Gastroenterology* 1977; **73**: 386–94.
6. Neuberger J, Portmann B, Nunnerley HB. Oral contraceptive associated liver tumours: occurrence of malignancy and difficulties in diagnosis. *Lancet* 1980; **i**: 273–6.
7. Iwatsuki S, Todo S, Starzl TE. Excisional therapy for benign hepatic lesions. *Surg Gynecol Obstet* 1990; **171**: 240–6.
8. Leese T, Farges O, Bismuth H. Liver cell adenomas: a 12 year surgical experience from a specialist hepato-biliary unit. *Ann Surg* 1988; **203**: 558–64.
9. Koelma IA, Nap M, Huitema S, Krom RAF, Houthoff HJ. Hepatocellular carcinoma, adenoma, and focal nodular hyperplasia. Comparative histopathologic study with immunohistochemical parameters. *Arch Pathol Lab Med* 1986; **110**: 1035–40.
10. Welch TJ, Sheedy PF, Johnson CM *et al.* Focal nodular hyperplasia and hepatic adenoma: comparison of angiography, CT, US, and scintigraphy. *Radiology* 1985; **156**: 593–5.
11. Mattison GR, Glazer GM, Quint LE, Francis IR, Bree RL, Ensminger WD. MR imaging of hepatic focal nodular hyperplasia: characterization and distinction from primary malignant hepatic tumors. *AJR Am J Roentgenol* 1987; **148**: 711–15.
12. Mathieu D, Bruneton JN, Drouillard J, Caron-Pontreau C, Vasile N. Hepatic adenomas and focal nodular hyperplasia: dynamic CT study. *Radiology* 1986; **292**: 1355–7.
13. Butch RJ, Stark DD, Malt RA. MR imaging of hepatic focal nodular hyperplasia. *J Comput Assist Tomogr* 1986; **10**: 874–7.
14. Anthony PP. Tumours and tumour like lesions of the liver and biliary tract. In: MacSween RNM, Anthony PP, Scheuer PJ, eds. *Pathology of the Liver.* 2nd ed. Edinburgh: Churchill Livingstone, 1987: 574–645.
15. Shortell CK, Schwartz SI. Hepatic adenoma and focal nodular hyperplasia. *Surg Gynecol Obstet* 1991; **173**: 426–31.
16. Edmonson HA, Henderson B, Benton B. Liver-cell adenomas associated with use of oral contraceptives. *N Engl J Med* 1976; **294**: 470–2.
17. Pain JA, Gimson AES, Williams R, Howard ER. Focal nodular hyperplasia of the liver: results of treatment and options in management. *Gut* 1991; **32**: 524–7.
18. Bennet WF, Bova JG. Review of hepatic imaging and a problem oriented approach to liver masses. *Hepatology* 1990; **12**: 761–75.
19. Vilgrain V, Fléjou JF, Arrivé L *et al.* Focal nodular hyperplasia of the liver: MR imaging and pathologic correlation in 37 patients. *Radiology* 1992; **184**: 699–703.
20. Coombs RJ, Woldenberg LS, Skeel RT, Bishara HM, Merrick HW. Magnetic resonance imaging of hepatic adenoma. *Clin Imaging* 1990; **14**: 44–7.
21. Lubbers PR, Ros PR, Goodman ZD, Ishak KG. Accumulation of technetium-99m sulfur colloid by hepatocellular adenoma: scintigraphic–pathologic correlation. *AJR Am J Roentgenol* 1987; **148**: 1105–8.
22. Edmonson HA, Reynolds TB, Henderson B, Benton B. Regression of liver cell adenomas associated with oral contraceptives. *Ann Intern Med* 1977; **86**: 180–2.
23. Buhler H, Pirovino M, Akovbiantz A *et al.* Regression of liver cell adenoma. A follow-up study of three consecutive patients after discontinuation of oral contraceptive use. *Gastroenterology* 1982; **82**: 534–6.
24. Gordon SC, Reddy KR, Livingstone AS. Resolution of a contraceptive steroid induced hepatic adenoma with subsequent evolution into hepatocellular carcinoma. *Ann Intern Med* 1986; **105**: 547–9.
25. Teitelbaum DH, Tuttle S, Carey LC, Clausen KP. Fibrolamellar carcinoma of the liver: review of three cases and the presentation of a characteristic set of tumor markers defining this tumor. *Ann Surg* 1985; **202**: 36–41.

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Clinical trial of tamoxifen in patients with irresectable pancreatic adenocarcinoma

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Oestrogen-binding sites are present in tissue samples of adenocarcinoma of the pancreas. Uncontrolled studies have suggested that survival of patients with this tumour may be extended by using the antioestrogen drug tamoxifen. Forty-four patients with biopsy-proven irresectable adenocarcinoma of the pancreas were recruited into a randomized placebo-controlled clinical trial of tamoxifen 20 mg twice daily. All patients were assessed at the time of diagnosis and at monthly intervals using the Karnofsky and the Hospital Anxiety and Depression scores for quality of life. Analysis of survival by life-tables and the log rank test revealed no significant difference in the duration of survival of patients treated with tamoxifen or placebo. Quality-of-life assessment revealed no significant difference between the groups. Tamoxifen does not confer significant benefit to patients with irresectable pancreatic cancer.

Adenocarcinoma of the exocrine pancreas is a distressing disease that is rarely cured. The majority of patients with this tumour are unsuitable for potentially curative surgical resection. Chemotherapy and radiotherapy do not offer significant benefit to patients with irresectable tumours[1,2]; combination therapy may have greater potential[3]. Survival is usually measured in months and jaundice, cachexia, anorexia and abdominal pain occur before death[4,5].

High-affinity oestrogen-binding sites in the pancreas of rats and in samples of human pancreatic adenocarcinoma suggest that pancreatic tumours might be susceptible to hormonal manipulation[6–8]. Two non-randomized studies of the oestrogen receptor antagonist tamoxifen in patients with irresectable cancer of the pancreas[9,10] have demonstrated a longer than expected survival in treated patients. A study of 14 patients from Birmingham, UK[11], however, used repeated computed tomography to assess disease progress and detected no response to treatment with tamoxifen.

A randomized controlled clinical trial was carried out to determine the influence of tamoxifen on the duration of survival and quality of life in patients with biopsy-proven irresectable cancer of the exocrine pancreas.

Patients and methods

Patients were recruited from the Yorkshire region, with a population of about 3·5 million and over 400 patients with pancreatic cancer registered annually[12]. The trial was managed and conducted by a coordinator who assessed, randomized and reviewed patients and completed all the documentation. Participating clinicians informed the coordinator of potentially eligible patients and arranged for biopsy to establish the diagnosis.

The study was designed as a prospective double-blind placebo-controlled trial with random allocation of either tamoxifen 20 mg twice daily or a similar dosage of an inert identical placebo tablet.

Running the trial

Abdominal ultrasonography and laparotomy were routinely used to stage the tumour, and computed tomography and endoscopic retrograde cholangiopancreatography employed when available. Diagnosis was confirmed histologically in tissue obtained by wedge or transduodenal needle biopsy at laparotomy, ultrasound-guided percutaneous needle biopsy or aspiration cytology. When possible, biopsy material was stored in liquid nitrogen for eventual oestrogen receptor analysis using a commercial kit (Abbott ER-ICA Monoclonal; Abbott Laboratories, Wokingham, UK).

At the first visit, each patient was interviewed and invited to complete a Hospital Anxiety and Depression (HAD) questionnaire[13], and the Karnofsky index[14] was calculated. These two scores were used as a measure of quality of life.

All randomized patients were followed at monthly intervals in the outpatient clinic of the local hospital by the coordinator. Assessment of the progress of disease was made by enquiry into symptoms, brief clinical examination, and HAD and Karnofsky scores. Follow-up continued for up to 18 months or until the patient died. The date of death was confirmed through the statistics of the Family Practitioner Committee or the Yorkshire Cancer Registry.

Eligibility criteria for randomization were as follows:

1. Histologically confirmed pancreatic adenocarcinoma.
2. Irresectable tumour.
3. Age 40–85 years.
4. Karnofsky score $\geqslant 50$.
5. No other previous or current malignant tumour other than basal cell carcinoma of the skin or *in situ* carcinoma of the cervix.
6. No previous treatment with tamoxifen or any other antioestrogen therapy.

The requirement for a Karnofsky score $\geqslant 50$ was included to prevent the randomization of patients who were so debilitated by the disease that survival would be very short.

Approval was obtained from the ethical committee of each participating hospital and informed consent given by all patients.

Statistical methods

Survival data were analysed using life-tables and the treatment arms compared using the log rank test. Quality-of-life scores were compared using the method of summary measures[15], which allowed a comparison of the overall change or trend (deterioration or improvement) of each treatment arm. Scores were compared separately at each monthly review using the Mann–Whitney U test.

Results

Between January 1987 and September 1988, 27 consultants in 14 hospitals informed the coordinator of 102 patients with probable pancreatic carcinoma. Biopsy was performed in 82 patients and confirmed this diagnosis in 59. Of the remaining 23 patients, an alternative diagnosis was revealed in 11 (chronic pancreatitis in three, gastric carcinoma in two, lymphoma in two, cholangiocarcinoma in two, tumour of the sphincter of Oddi in one, neuroendocrine tumour in one). Ten patients

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Table 1 *Characteristics of randomized patients and quality of life at initial assessment*

	Tamoxifen ($n = 22$)	Placebo ($n = 22$)
Age (years)*	64 (48–83)	65 (40–81)
F	8	13†
M	14	9†
Karnofsky score*	70 (50–90)	70 (50–90)
Anxiety score*	5 (1–14)	6 (1–20)
Depression score*	5 (1–11)	5 (1–15)

*Values are median (range); $P > 0{\cdot}05$ (Mann–Whitney U test). †$P > 0{\cdot}05$ (χ^2 test)

Table 2 *Clinical features of randomized patients*

	Tamoxifen ($n = 22$)	Placebo ($n = 22$)
Operation		
None	4	4
Laparotomy only	3	5
Bypass procedure	14	11
Partial resection	1	2
Tumour stage*		
T_1	1	2
T_2	5	5
T_3	15	15
T_x	1	0
Metastases	9	8
Histological grade		
Well differentiated	4	3
Moderately differentiated	8	7
Poorly differentiated	4	7
Not specified	6	5

*T_1, tumour limited to pancreas; T_2, extension limited to duodenum, bile duct or stomach; T_3, further direct extension; T_x, not assessable

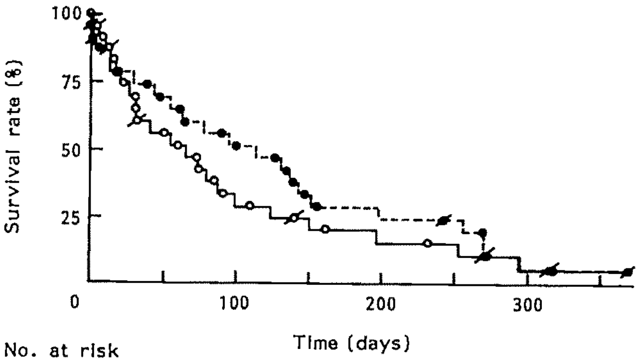
underwent biopsies that were equivocal, and in two patients attempts at biopsy failed.

Twenty patients did not undergo biopsy. The surgeon considered it unnecessary to confirm the diagnosis in 13 who were excluded from the trial. In five other patients an alternative diagnosis became evident without the need for biopsy. In a further two patients biopsy was not performed because it was considered too hazardous or because the patient was thought to be too ill. No patient developed a serious complication attributable to biopsy.

In 25 patients, biopsy material was collected for oestrogen receptor analysis. No tumour exhibited even low levels of the specific receptor identified by the monoclonal antibody supplied in the ER-ICA kit.

Only patients with a histologically confirmed diagnosis of adenocarcinoma of the pancreas were considered for randomization. In all, 44 were randomized (including one patient subsequently found to have a lymphoma). Of the remaining 16 patients, six had a Karnofsky score <50, in four cases the clinician wished the patient to be treated with tamoxifen (precluding randomization), three patients underwent a potentially curative resection and were thus ineligible, and one patient declined randomization. The remaining two patients were seen at the beginning of recruitment and could not be randomized because of the lack of trial medication at that time, but are included for completeness.

Of the 44 randomized patients, five withdrew from the trial but were included in the final analysis (three were allocated tamoxifen and two placebo). Two of the withdrawals, both receiving tamoxifen, stopped taking medication within 14 days because of nausea. One patient changed a decision to participate after randomization. One patient suffered a fatal haemorrhage from the pancreas before the allocated medication was started. The fifth was withdrawn because of a change in diagnosis.



No. at risk								
Tamoxifen	22	13	7	5	4	2	1	0
Placebo	22	15	12	7	6	5	2	1

Figure 1 *Life-table analysis of patients treated with tamoxifen* (○) *or placebo* (●). *ø and* ⌀, *censored results.* P = *0·3* (*log rank test*)

Twenty-two patients received tamoxifen and the same number placebo. The median age and Karnofsky and HAD scores in the two groups were similar at the time of randomization (*Table 1*). Tumour node metastasis stage, tumour grade and the surgery performed on patients in the two groups were also similar (*Table 2*).

The duration of survival was calculated as the time from the day of randomization to death or to the last follow-up visit if death had not occurred (censored results). The survival data are plotted using life-tables and compared by the log rank test (*Figure 1*). The calculated median survival time of patients in the placebo group was 131 (interquartile range 48–156) days and that of patients in the tamoxifen-treated group 75 (interquartile range 32–139) days. There was no statistically significant difference between the two life-tables ($P = 0{\cdot}3$, log rank test). Calculation of the survival difference at 90 days produced an estimated increased survival proportion in the tamoxifen-treated group of −22 per cent (95 per cent confidence interval −53 to 8·6 per cent).

The median scores of quality of life in the two groups were compared at each monthly review and no significant difference was found at any time. A more representative comparison of individual longitudinal data is difficult, but the method of summary measures described by Matthews *et al.*[15] is a valid technique. Using this method, the rate of change in quality-of-life scores during the trial for each patient was calculated by linear regression analysis. These summary measures were then compared by the Mann–Whitney U test and again no statistically significant difference was apparent.

Discussion

Carcinoma of the pancreas is a common condition in the UK (approximately 100 cases per million population annually). Trials of treatment have often included relatively few patients[6–8]. This trial was designed to minimize disruption to patient and participating clinician, with the coordinator performing all administrative and clinical duties. Only 44 patients were randomized during the 2 years of the trial despite 102 patient referrals. The recruitment rate (43 per cent) was not unusually low for a clinical trial of this type[16].

The rate of biopsy was relatively high for the region. Only 16 per cent of cases registered in the regional cancer registry in 1983 as pancreatic carcinoma were histologically confirmed, compared with 70 per cent in this study. No significant complications attributable to biopsy were encountered, and the clinical diagnosis of adenocarcinoma was changed as a result of biopsy in 11 cases. The use of biopsy is to be encouraged.

It is regrettable that a relatively small number of patients were randomized. This is reflected in the wide 95 per cent confidence interval for the calculated survival difference at 90 days. This does indicate, however, that a survival advantage due to tamoxifen greater than 9 per cent at 90 days was unlikely ($P < 0{\cdot}05$). In view of the enormous difficulty in recruitment of patients and running of the study, continuation did not seem justified.

The negative result of this study is supported by a recent report from Norway[17], in which 176 patients were randomized to receive tamoxifen or placebo. No statistically significant difference in duration of survival was found, but quality-of-life assessments and oestrogen receptor assays were not performed.

The combination of an assessment of the capacity to perform everyday activities (Karnofsky score) and an assessment of psychological well-being (HAD score) was chosen to represent a measure of the quality of life. No significant difference between the two treatment arms was seen.

The lack of evidence of an influence of tamoxifen on the natural history of pancreatic adenocarcinoma from two randomized studies in the light of negative oestrogen receptor analysis is not surprising. Despite its safety and relatively low cost, tamoxifen does not have a proven role in the treatment of pancreatic cancer.

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References

1. The Gastrointestinal Tumor Study Group. Phase II studies of drug combinations in advanced pancreatic carcinoma: fluorouracil plus doxorubicin plus mitomycin C and two regimens of streptozotocin plus mitomycin C plus fluorouracil. *J Clin Oncol* 1986; **4**: 1794–8.
2. Dobelbower RR, Milligan AJ. Treatment of pancreatic cancer by radiation therapy. *World J Surg* 1984; **8**: 919–28.
3. The Gastrointestinal Tumor Study Group. Treatment of locally unresectable carcinoma of the pancreas: comparison of combined-modality therapy (chemotherapy plus radiotherapy) to chemotherapy alone. *J Natl Cancer Inst* 1988; **80**: 751–5.
4. Williamson RCN. Pancreatic cancer: the greatest oncological challenge. *BMJ* 1988; **296**: 445–6.
5. Livstone EM, Spiro HM. The pancreatic cancer problem. *World J Surg* 1984; **8**: 803–7.
6. Sandberg AA, Rosenthal HE. Estrogen receptors in the pancreas. *J Steroid Biochem* 1974; **5**: 969–75.
7. Stedman KE, Moore GE, Morgan RT. Estrogen receptor proteins in diverse human tumors. *Arch Surg* 1980; **115**: 244–8.
8. Greenway B, Iqbal MJ, Johnson PJ, Williams R. Oestrogen receptor proteins in malignant and fetal pancreas. *BMJ* 1981; **283**: 751–3.
9. Theve NO, Pousette A, Carlstrom K. Adenocarcinoma of the pancreas – a hormone sensitive tumour? A preliminary report on Nolvadex treatment. *Clin Oncol* 1983; **9**: 193–7.
10. Tonnesen K, Kamp-Jensen M. Antiestrogen therapy in pancreatic carcinoma: a preliminary report. *Eur J Surg Oncol* 1986; **12**: 69–70.
11. Crowson MC, Dorrell A, Rolfe EB, Fielding JWL. A phase II study to evaluate tamoxifen in pancreatic adenocarcinoma. *Eur J Surg Oncol* 1986; **12**: 335–6.
12. Yorkshire Regional Cancer Registry. *Yorkshire Regional Cancer Organization. Report for the Year 1985 Including Cancer Statistics for 1978–83*. Leeds: Yorkshire Regional Cancer Registry, 1985.
13. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression scale. *Acta Psychiatr Scand* 1983; **67**: 361–70.
14. Karnofsky DA, Burchenal JH. The clinical evaluation of chemotherapeutic agents against cancer. In: McLeod CM, ed. *Evaluation of Chemotherapeutic Agents, Symposium Section on Microbiology*. New York: Columbia University Press, 1949: 191–205.
15. Matthews JNS, Altman DG, Campbell MJ, Royston P. Analysis of serial measurements in medical research. *BMJ* 1990; **300**: 230–5.
16. Hunter CP, Frelick RW, Feldman AR *et al.* Selection factors in clinical trials: results from the Community Clinical Oncology Program physician's patient log. *Cancer Treat Rep* 1987; **71**: 559–65.
17. Bakkevold KE, Pettersen A, Arnesjo B, Espehaug B. Tamoxifen therapy in unresectable adenocarcinoma of the pancreas and the papilla of Vater. *Br J Surg* 1990; **77**: 725–30.

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Suppression of macrophage function by suture materials and anastomotic recurrence of Crohn's disease

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After surgical excision of bowel, Crohn's disease is likely to recur around the anastomosis. It is suggested that this may indicate a biological effect of suture materials on gastrointestinal immunology. To investigate this, the influence of six suture materials on the function of macrophages obtained from the rat peritoneal cavity and human intestinal mucosa was assessed. All materials significantly impaired macrophage function.

Until recently sutures used for anastomosis were examined only for handling qualities, tensile strength and effects on sepsis and anastomotic healing. A differential effect of various suture materials in enhancing local carcinogenesis in experimental colorectal cancer has now been demonstrated, although it has not been agreed which materials are good or bad[1,2]; this lack of consensus may stem from differences in study design. Nevertheless, the demonstration that suture materials might contribute to disease recurrence at an anastomosis is important.

Anastomotic recurrence is also frequently seen in patients with Crohn's disease. Rutgeerts *et al.*[3] showed that within 1 year of right hemicolectomy for this disease there was endoscopically proven anastomotic recurrence in >70 per cent of patients. In large bowel Crohn's disease, colectomy with ileorectal anastomosis carries a 60 per cent chance of further surgery for recurrent disease by 20 years, whereas proctocolectomy with an end ileostomy and no anastomosis carries only a 20 per cent risk[4]. The presence of an anastomosis seems to predispose to recurrent Crohn's disease.

One of the cell types fundamentally involved in the mucosal immunology of the gastrointestinal tract is the macrophage[5]; this cell has an established position in Crohn's disease[6] and may play a role in carcinogenesis[7]. The *in vitro* effect of a range of suture materials on macrophage function in both a rodent model and humans undergoing intestinal resection was therefore examined.

Patients and methods

Macrophages were obtained from the rat peritoneal cavity and human intestinal mucosa. During the isolation procedures only plastic tubes and culture bottles were used because these cells adhere readily to glass and may become activated. Functional studies were then performed and the effect of suture materials on macrophage functions assessed.

Cell procurement

Rat. Seven healthy male rats were killed. The abdomen was immediately swabbed with alcohol and the skin incised and retracted to expose the abdominal wall. Cold Hanks' balanced salt solution (15 ml) was injected rapidly into the peritoneal cavity via the anterior midline. After gently massaging the abdomen for several minutes the peritoneal cavity was opened through a midline incision. The gut was retracted and the peritoneal fluid aspirated from the paracolic gutters and pelvis with a syringe. This fluid was transferred to a sterile centrifuge tube and stored on ice; 0·5 ml of this suspension was removed and the number of cells present in this sample counted using a haemocytometer. At this stage a viability test was performed using the trypan blue exclusion technique. The original cell suspension was then centrifuged at 170*g* for 10 min at 4°C. The supernatant was discarded and the pellet of macrophages resuspended in RPMI with antibiotics. The washing step was repeated and the macrophages resuspended in suture-primed medium.

Human. Intestinal macrophages were obtained by mucosal enzymatic digestion using an established method[8]. Six patients undergoing intestinal resection at St Mark's Hospital were studied. Immediately after resection, the specimen was opened and washed. A full-thickness strip of bowel wall up to 5 × 2 cm in area was removed, usually along the edge of the specimen, and placed in ice-cold RPMI 1640 tissue culture medium containing 20 mmol/l Hepes, 24 mmol/l sodium bicarbonate, 100 units/ml penicillin, 0·1 mg/ml streptomycin, 80 µg/ml gentamicin and 2 µg/ml Fungizone (Squibb, Hounslow, UK). The isolation procedures described below were initiated within 60 (usually 30) min of resection.

Using sterile technique the intestinal mucosa was dissected free from the muscularis mucosae, washed several times in calcium- and magnesium-free Hanks' balanced salt solution (CMF–HBSS) and cut into small fragments. These were washed thoroughly and incubated in ethylenediamine tetra-acetic acid (EDTA) to remove the epithelial cells from the lamina propria. The EDTA incubation was repeated twice with extensive washing in CMF–HBSS between each incubation period. The fragments of exposed lamina propria were then incubated overnight at 37°C in an atmosphere of 5 per cent carbon dioxide in air, with continuous shaking, in RPMI 1640 containing 10 per cent fetal calf serum, 20 mg per 100 ml collagenase (from *Clostridium histolyticum*; Boehringer Mannheim, Lewes, UK or Sigma Chemicals, Poole, UK) and 1000 units DNAse. The incubate was filtered through a 100-µm nylon mesh (Gallenkamp, Loughborough, UK) to remove undigested tissue and the cells then centrifuged at 400*g* for 15 min at room temperature. The pellet obtained was resuspended in 5 ml RPMI 1640.

Mononuclear cells were obtained by density-gradient centrifugation on Histopaque-1077 (Sigma). Viability was assessed at this stage using trypan blue exclusion; immunoperoxidase staining of a cytospin preparation with the monoclonal antibody EBM11 (Dakopatts, Glostrup, Denmark) was used to calculate the proportion of macrophages in the suspension.

Preparation of suture-primed medium

The suture materials studied were Ethilon (nylon), Mersilk (silk), chromic catgut, steel wire, coated Vicryl (polyglactin 910) and PDS (polydioxanone) (all Ethicon, Edinburgh, UK). A single length of 5/0 suture material was allowed to dry, placed in 15 ml RPMI with antibiotics and then incubated with agitation for 48 h at 37°C. The suture material was then removed and the pH of the fluid measured. The tissue culture fluid was stored at 4°C until required, usually within 24 h. Control medium was prepared in the same way without the addition of suture material.

Assays of adherence and phagocytosis

A monolayer of adherent macrophages was created by pipetting 2 ml cell suspension (macrophages in suture-primed or control medium) into a Leighton tube containing a Leighton cover-slip. For the adherence assay, the cover-slip was removed after incubation in 5 per cent carbon dioxide at 37°C for 2 h, non-adherent cells washed away and adherent cells fixed, stained and counted. For the assay of phagocytosis, after the 2-h incubation period zymosan was added to the tube which was returned to the incubator for 1 h. Excess zymosan and non-adherent cells were then washed away and the adherent cells fixed, stained and counted. Cells containing two or more particles of zymosan were counted as positive, while those containing one particle or none were regarded as negative. The ratio of positive cells to total cell number was then expressed as the phagocytic index.

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Table 1 *Suture material and adherence in rats*

	No. of adherent cells							
	Experiment no.							
Suture material	1	2	3	6	7	8	9	Mean (%)
Control	655 (100)	1223 (100)	512 (100)	199 (100)	1191 (100)	127 (100)	606 (100)	100
Nylon (Ethilon)	518 (79·1)	675 (55·2)	308 (60·1)	114 (57·3)	485 (40·7)	110 (86·6)	73 (12·0)	55·0*
Polyglactin 910 (Vicryl)	314 (47·9)	872 (71·3)		84 (42·2)	590 (49·5)	126 (99·2)	221 (36·5)	57·7*
Polydioxanone (PDS)	375 (57·3)	516 (42·2)	298 (58·1)		423 (35·5)	102 (80·3)	209 (34·5)	51·3*
Silk	380 (58·0)	120 (9·8)		154 (77·4)	669 (56·2)	81 (63·8)	459 (75·7)	56·7*
Catgut	123 (18·8)	291 (23·8)	72 (14·1)	89 (44·7)	414 (34·8)		139 (22·9)	26·5*
Steel	71 (10·8)	157 (12·8)	285 (55·6)		768 (64·5)	99·5 (78·3)	519 (85·6)	51·4*

Values in parentheses are percentages of control value. *$P < 0·05$ *versus* control (Mann–Whitney *U* test)

Table 2 *Suture material and lactic dehydrogenase leakage in rats*

	Lactic dehydrogenase absorbance (arbitrary units)							
	Experiment no.							
Suture material	1	2	3	4	5	6	7	Mean (%)
Control	39 (100)	37 (100)	20 (100)	32 (100)	17 (100)	86 (100)	15 (100)	100
Nylon (Ethilon)	28 (72)	32 (86)	13 (65)	20 (62)	17 (100)	71 (83)	16 (107)	82·1*
Polyglactin 910 (Vicryl)	19 (49)			24 (75)	15 (88)	89 (103)	4 (27)	69·1
Polydioxanone (PDS)	18 (46)	43 (116)	20 (100)	68 (212)	19 (112)	96 (112)	15 (100)	113·9
Silk	15 (38)	42 (114)		67 (209)	14 (82)		13 (87)	106·6
Catgut	15 (38)		19 (95)		19 (112)	89 (103)	10 (67)	84·0
Steel	14 (36)	87 (235)	21 (105)		18 (106)		11 (73)	112·1

Values in parentheses are percentages of control value. *$P < 0·05$ *versus* control (Mann–Whitney *U* test)

Table 3 *Suture material and lysozyme secretion in rats*

	Lysozyme secretion (arbitrary units)					
	Experiment no.					
Suture material	1	2	3	4	5	Mean (%)
Control	56·7 (100)	66·9 (100)	32·0 (100)	12·0 (100)	30·0 (100)	100
Nylon (Ethilon)	33·3 (58·8)	46·9 (70·1)	30·0 (93·8)	9·0 (75·0)	31·0 (103·3)	80·2
Polyglactin 910 (Vicryl)	41·3 (72·8)		48·0 (150)	5·5 (45·8)	58·0 (193·3)	115·0
Polydioxanone (PDS)	53·0 (93·5)	51·3 (76·7)	37·0 (115·6)	7·8 (64·6)	31·0 (103·3)	90·7
Silk	46·6 (82·2)		27·5 (85·9)	4·5 (37·5)	28·0 (93·3)	74·7*
Catgut	48·3 (85·2)	45·8 (68·5)		6·5 (54·2)	22·0 (73·3)	70·3*
Steel	35·0 (61·7)	47·5 (71·0)		8·3 (69·2)		67·3

Values in parentheses are percentages of control value. *$P < 0·05$ *versus* control (Mann–Whitney *U* test)

Table 4 *Suture material and phagocytosis in rats*

	Phagocytic index					
	Experiment no.					
Suture material	1	2	3	4	5	Mean (%)
Control	66·4 (100)	59·0 (100)	59·5 (100)	22·5 (100)	27·0 (100)	100
Nylon (Ethilon)	65·4 (98·5)	47·7 (80·9)	60·1 (100·9)	23·0 (102·2)	34·0 (125·9)	101·7
Polyglactin 910 (Vicryl)	55·6 (83·8)	40·2 (68·2)	59·2 (99·5)	18·5 (82·2)	26·0 (96·3)	86·0
Polydioxanone (PDS)	55·3 (83·3)	40·0 (67·8)	48·3 (81·1)	13·5 (60·0)	29·0 (107·4)	80·0
Silk	40·0 (60·3)	41·1 (69·7)	57·1 (95·9)	15·5 (68·9)	33·0 (122·2)	83·4
Catgut	62·8 (94·6)	46·2 (78·3)	63·5 (106·7)	20·5 (91·1)	24·0 (88·9)	91·9
Steel	36·3 (54·6)	36·3 (61·6)	61·0 (102·5)	19·0 (84·4)	34·0 (125·9)	85·8

Values in parentheses are percentages of control value

Assay of secretory activity

Lysozyme was chosen as the secretory product to be measured; 2 ml cell suspension (macrophages in suture-primed or control medium) was placed in a sterile test tube which was then incubated in 5 per cent carbon dioxide at 37°C for 48 h. The lysozyme content of the supernatant was measured spectrophotometrically at 450 nm using established techniques[9].

Assessment of cell damage

The degree of cell damage was assessed by measuring the amount of lactic dehydrogenase (LDH) in the medium after incubating 2 ml cell suspension in a sterile test tube in 5 per cent carbon dioxide at 37°C for 48 h. In the presence of reduced nicotinamide adenine dinucleotide (NADH), LDH reduces pyruvic acid, resulting in the oxidation of NADH. The rate of oxidation of NADH is measured spectrophotometrically at 340 nm and is proportional to the activity of LDH in the specimen.

Table 5 *Suture material and macrophage function in rats*

Suture material	Adherence ($n = 6$)	LDH leakage ($n = 7$)	Lysozyme secretion ($n = 7$)	Phagocytosis ($n = 5$)
Control	100	100	100	100
Nylon (Ethilon)	55·0*	82·1*	80·2	101·7
Polyglactin 910 (Vicryl)	57·7*	69·1	115·0	86·0
Polydioxanone (PDS)	51·3*	113·9	90·7	80·0
Silk	56·7*	106·6	74·7*	83·4
Catgut	26·5*	84·0	70·3*	91·9
Steel	51·4*	112·1	67·3	85·8

Values are mean percentages of control. LDH, lactic dehydrogenase. $^{*}P < 0·05$ *versus* control (Mann–Whitney U test)

Results

Rat

The proportion of macrophages in the crude peritoneal cell suspension varied from 60 to 70 per cent. However, this increased to >95 per cent by creating a monolayer of adherent cells before performing any functional studies. The viability of the macrophages was never <90 per cent and the pH of the suture-primed media did not differ significantly from that of controls.

The results of the functional studies are shown in detail in *Tables 1–4* and summarized in *Table 5*. It can be seen that all suture materials produced a significant reduction in adherence compared with controls. Cell damage in culture, as assessed by LDH leakage, was significantly less in medium primed with nylon than in control medium. Lysozyme secretion was significantly impaired by catgut and silk. It is possible that some lysozyme activity in the supernatants represents the release of preformed protein from damaged cells but the effect of suture materials on lysozyme concentrations is different from that on LDH leakage (a measure of cell damage) and it is, therefore, more likely that the changes in lysozyme level represent largely an alteration in active secretion.

Humans

Cell viability, as assessed by trypan blue exclusion, was a mean 76 (range 70–84) per cent. The proportion of macrophages in the mononuclear cell suspension was similar in all groups, with a mean of 20 (range 18–22) per cent in the small bowel and 18 (range 16–22) per cent in the large intestine. The functional studies therefore demonstrate the effect of suture materials on both macrophages and contaminating lymphocytes. The results of the functional studies are shown in detail in *Tables 6–8* and summarized in *Table 9*. All materials impaired macrophage

Table 6 *Suture material and adherence in humans*

	Adherent cells as a proportion of total no. of cells in specimen						
	Experiment no.						
Suture material	1	2	3	4	5	6	7
Control	0·5 (100)	1·1 (100)	0·8 (100)	0·9 (100)	0·6 (100)	1·2 (100)	0·3 (100)
Steel	0·2 (39)	0·6 (58)	0·5 (61)	0·4 (49)	0·2 (39)	1·4 (121)	0·2 (56)
Polydioxanone (PDS)	0·5 (96)	0·7 (68)	0·8 (94)	1·0 (115)	0·4 (61)	1·0 (84)	0·3 (94)
Polyglactin 910 (Vicryl)	0·1 (29)	0·9 (85)	0·7 (85)	0·5 (56)	0·3 (52)	1·2 (100)	0·2 (63)
Silk	0·4 (82)	1·1 (103)	0·8 (97)	0·7 (84)	0·3 (58)	1·1 (88)	
Catgut		0·8 (77)	0·6 (73)	0·8 (89)	0·3 (42)	1·3 (109)	0·3 (88)
Nylon (Ethilon)	0·2 (46)		0·7 (82)	0·8 (95)	0·5 (82)	0·4 (35)	0·3 (81)

Values in parentheses are percentages of control value

Table 7 *Suture material and lactic dehydrogenase leakage in humans*

	Lactic dehydrogenase absorbance (arbitrary units)						
	Experiment no.						
Suture material	1	2	3	4	5	6	7
Control	13·2 (100)	15·7 (100)	12·7 (100)	8·5 (100)	25·0 (100)	40·7 (100)	18·8 (100)
Steel	20·4 (155)	12·3 (78)	14·2 (112)		25·0 (100)	30·0 (74)	37·5 (199)
Polydioxanone (PDS)	33·2 (252)		19·2 (151)	11·5 (135)	20·8 (83)	16·0 (39)	17·1 (91)
Polyglactin 910 (Vicryl)	17·2 (130)	14·3 (91)	19·2 (151)	4·1 (48)	19·6 (78)		15·8 (84)
Silk	10·8 (82)	16·7 (106)	20·4 (161)	14·1 (166)	25·0 (100)	47·3 (116)	11·3 (60)
Catgut	12·8 (97)	15·7 (100)		14·7 (173)	12·1 (48)	20·0 (49)	10·8 (57)
Nylon		11·7 (75)	20·4 (161)	18·2 (214)	5·4 (22)	78·0 (192)	22·1 (118)

Values in parentheses are percentages of control value

Table 8 *Suture material and lysozyme secretion in humans*

	Lysozyme secretion (arbitrary units)						
	Experiment no.						
Suture material	1	2	3	4	5	6	Mean (%)
Control	2·8 (100)	2·3 (100)	1·2 (100)	5·6 (100)	6·0 (100)	5·4 (100)	100
Steel	0·8 (29)		1·2 (100)	0·3 (5)	2·7 (45)	0·8 (15)	39
Polydioxanone (PDS)	1·6 (57)	1·0 (43)	2·7 (225)	2·6 (46)		3·3 (61)	86
Polyglactin 910 (Vicryl)	4·8 (171)	1·0 (43)	1·2 (100)	3·2 (57)	9·3 (155)	2·1 (39)	94
Silk	2·8 (100)	2·3 (100)	0·0 (0)		2·0 (33)	4·6 (85)	80
Catgut	1·2 (43)	7·0 (304)	1·9 (158)	1·2 (21)	3·3 (55)		116
Nylon (Ethilon)	2·0 (71)	2·0 (87)		5·0 (89)	6·7 (112)	1·7 (31)	78

Values in parentheses are percentages of control values

Table 9 *Suture material and macrophage function in humans*

Suture material	Adherence ($n = 6$)	LDH leakage ($n = 6$)	Lysozyme secretion ($n = 6$)
Control	100	100	100
Nylon (Ethilon)	70*	130	78
Polyglactin 910 (Vicryl)	67*	97	94
Polydioxanone (PDS)	87*	125	86
Catgut	80*	87	116
Silk	85*	113	80
Steel	60*	120	39

Values are mean percentages of control. Phagocytosis studies were not performed. LDH, lactic dehydrogenase. $^*P < 0{\cdot}01$ *versus* control (Mann–Whitney U test)

adherence and the difference between controls and the combined suture materials was significant ($P < 0{\cdot}01$, Wilcoxon rank sum test); steel had the most pronounced effect on both lysozyme secretion and adherence.

Discussion

The results of the present study demonstrate that suture materials influence macrophage function *in vitro*. If the same were to happen *in vivo*, this would imply that macrophages in the vicinity of an anastomosis after intestinal resection for Crohn's disease may influence the risk of local recurrence. This would be consistent with earlier studies that suggest the risk of recurrence is lower when granulomas and, therefore, macrophages are prominent in the resected specimen[10,11]. However, other studies have not confirmed this finding[12,13]; one explanation for the apparent contradiction is that macrophage number and histological appearance may be less related to the development of recurrent disease than is macrophage function.

Macrophages need to be healthy and capable of reaching the site of inflammation[14] where they can engulf particulate matter and kill bacteria. Adherence and lysozyme secretion indicate preparation for action and bacterial killing; in the present study these two functions were the most disturbed by preincubation of tissue culture medium with suture materials. Phagocytic capacity, on the other hand (which was tested only with rat macrophages), seemed relatively unaffected.

As all the materials affected adherence adversely, it is possible that contaminants left on the surface of the suture during production or integral to their structure were responsible. It has been shown that particulate metals of the type used in orthopaedic prostheses affect macrophage secretion[15] and phagocytosis[16], and some of the metals used in the manufacture of suture materials have similar effects[17]. Trace elements such as iron and zinc are known to be vitally important to immune function, probably because of their central role in membrane transport in lymphocytes and macrophages. In addition, it is now well established that toxic metals such as lead, chromium and nickel produce disturbances in a variety of macrophage functions, including phagocytosis and enzyme secretion[17]. Nickel has been shown to reduce the secretion of lysozyme by rabbit lung macrophages and to produce morphological changes, although these did not appear to affect adherence[18]. Copper and aluminium have been shown to produce significant impairment of phagocyte function in other species[19], and it has recently been suggested that aluminium produces clinically significant immunosuppression in humans[20] and can reduce the incidence of rejection after renal transplantation[21].

Recurrent Crohn's disease is more frequently seen on the small bowel side of an ileocolic anastomosis[22–24]. Attempts to explain this have invoked functional obstruction at the anastomosis with proximal stasis (which might be circumvented by performing a wider side-to-side anastomosis) and reflux of colonic content into the neoterminal ileum[25] (which might be prevented by nipple-valve construction at the site of anastomosis). Another explanation, which would be supported by the present study, is that disease recurs in the mucosal lymphoid areas (Peyer's patches) which are denser in the small bowel than in the colon.

The involvement of mucosal macrophages in the pathogenesis of Crohn's disease is well established. The possibility that metals may be involved in the impairment of macrophage function by suture materials is particularly relevant to Crohn's disease because aluminium, silicon and titanium have been found in Peyer's patch macrophages in the terminal ileum of both patients with Crohn's disease and normal controls[26]. It is suggested that, since aluminium[27] and titanium[28] are known to produce granulomatous lesions in the human lung, these metals may be involved in the pathogenesis of Crohn's disease[26]. These metals and others are present in modern suture materials, at least during their preparation, and they may, therefore, be implicated in the pathogenesis of locally recurrent Crohn's disease at surgical anastomoses.

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References

1. Phillips RKS, Cook HT. Effect of steel wire sutures on the incidence of chemically induced rodent colonic tumours. *Br J Surg* 1986; 73: 671–4.
2. McGregor JR, Galloway DJ, McCulloch P, George WD. Anastomotic suture materials and implantation metastasis: an experimental study. *Br J Surg* 1989; 76: 331–4.
3. Rutgeerts P, Geboes K, Vantrappen G, Kerremans R, Coenegrachts JL, Coremans G. Natural history of recurrent

Crohn's disease at the ileocolonic anastomosis after curative surgery. *Gut* 1984; **25**: 665–72.
4. Ritchie JK. The results of surgery for large bowel Crohn's disease. *Ann R Coll Surg Engl* 1990; **72**: 155–7.
5. Hodgson HJF, Jewell DP. Immunology of inflammatory bowel disease. *Baillieres Clin Gastroenterol* 1987; **1**: 531–45.
6. Lockhart-Mummery HE, Morson BC. Crohn's disease of the large intestine. *Gut* 1964; **5**: 493–509.
7. Munzarova M, Kovarik J. Is cancer a macrophage-mediated autoaggressive disease? *Lancet* 1987; **i**: 952–4.
8. Golder JP, Doe WF. Isolation and preliminary characterisation of human intestinal macrophages. *Gastroenterology* 1983; **84**: 795–802.
9. Litwack G. Photometric determination of lysozyme activity. *Proc Soc Exp Biol Med* 1955; **89**: 401–3.
10. Chambers TJ, Morson BC. The granuloma in Crohn's disease. *Gut* 1979; **20**: 269–74.
11. Softley A, Myren J, Clamp SE, Bouchier IAD, Watkinson G, de Dombal FT. Factors affecting recurrence after surgery for Crohn's disease. *Scand J Gastroenterol Suppl* 1988; **23**: 31–4.
12. Wolfson DM, Sachar DB, Cohen A *et al.* Granulomas do not affect postoperative recurrence rates in Crohn's disease. *Gastroenterology* 1982; **83**: 405–9.
13. Heimann TM, Miller F, Martinelli G, Szporn A, Greenstein AJ, Aufses AH Jr. Correlation of presence of granulomas with clinical and immunologic variables in Crohn's disease. *Arch Surg* 1988; **123**: 46–8.
14. Hermanowicz A, Gibson PR, Pallone F, Mason CH, Jewell DP. The function *in vitro* of macrophages from the intestinal mucosa of patients with Crohn's disease: an association between chemotactic migration and granulomata. *J Gastroenterol Hepatol* 1988; **3**: 117–25.
15. Rae T. The biological response to titanium and titanium–aluminium–vanadium alloy particles. *Biomaterials* 1986; **7**: 30–6.
16. Rae T. A study on the effects of particulate metals of orthopaedic interest on murine macrophages *in vitro*. *J Bone Joint Surg [Br]* 1975; **57-B**: 444–50.
17. Jaremin B. Immunoregulatory properties of some heavy metals in physiology and pathology. *Bull Inst Marit Trop Med Gdynia* 1985; **36**: 81–101.
18. Lungborg M, Johansson A, Camner P. Morphology and release of lysozyme following exposure of rabbit lung macrophages to nickel or cadmium *in vitro*. *Toxicology* 1987; **46**: 191–203.
19. Elsasser MS, Robertson BS, Hetrick FM. Effects of metals on the chemiluminescent response of rainbow trout (*Salmo gairdneri*) phagocytes. *Vet Immunol Immunopathol* 1986; **12**: 243–50.
20. Davenport A, Davison AM, Will EJ, Toothill C, Newton KE, Giles GR. Aluminium accumulation and immunosuppression. *BMJ* 1989; **298**: 458–9.
21. Nordal KP, Dahl E, Albrechtsen D *et al.* Aluminium accumulation and immunosuppressive effect in recipients of kidney transplants. *BMJ* 1988; **297**: 1581–2.
22. Alexander-Williams J, Fielding JF, Cooke WT. A comparison of results of excision and bypass for ileal Crohn's disease. *Gut* 1972; **13**: 973–5.
23. Goligher JC. Inflammatory disease of the bowel. Results of resection for Crohn's disease. *Dis Colon Rectum* 1976; **19**: 584–7.
24. Farmer RG, Hawk WA, Turnbull RB. Clinical patterns in Crohn's disease. A statistical study of 615 cases. *Gastroenterology* 1975; **68**: 627–35.
25. Burman JH, Thompson H, Cooke WT, Alexander-Williams J. The effects of diversion of intestinal contents on the progress of Crohn's disease of the large bowel. *Gut* 1971; **12**: 11–15.
26. Shepherd NA, Crocker PR, Smith AP, Levison DA. Exogenous pigment in Peyer's patches. *Hum Pathol* 1987; **18**: 50–4.
27. Chen WJ, Monnat RJ Jr, Chen M, Mottet NK. Aluminium induced pulmonary granulomatosis. *Hum Pathol* 1978; **9**: 705–11.
28. Shigematsu N, Matsuba K, Watanabe K. A granulomatous lung disease produced by titanium. In: Jones Williams W, Davies BH, eds. *Sarcoidosis and Other Granulomatous Diseases*. Cardiff: Alpha Omega, 1980: 728–33.

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Sphincter rupture in childbirth

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Thirty-eight women with rupture of the anal sphincter occurring during childbirth were followed for 3–12 months. Nineteen had complete rupture of the external anal sphincter, 14 had a lesion involving more than half of the sphincter muscle and five had a superficial rupture. Fourteen patients presented with continence disturbances: nine to solid or liquid faeces and five to flatus. Incontinence was present in nine women 3 months after childbirth. Anal manometry and electromyography were performed in patients 3–5 days after delivery and repeated at 3, 6 and 12 months. Manometry and electromyography were also performed in 16 control subjects who were nulliparous or had given birth more than 2 years previously and 24 primiparous controls, who were investigated at 3–5 days and at 3 months. There were significant differences between both incontinent and continent patients compared with nulliparous and primiparous controls. Primiparous control subjects had decreased anal squeeze pressure as well as decreased electromyographic activity on the first days after delivery compared with nulliparous controls. After 3 months no differences were found. Continence disturbances are frequent after sphincter rupture; these patients should be monitored after delivery and those with persisting incontinence offered sphincter repair.

Perineal laceration is a frequent complication of vaginal delivery. Most of the lesions include only the perineal skin or the bulbocavernous muscle, but in 0·7 per cent of cases the external anal sphincter is involved and persistent symptoms occur at a high rate in these patients[1].

This study presents the results of a 1-year follow-up of 38 patients with sphincter rupture occurring during childbirth.

Patients and methods

Thirty-eight consecutive patients of median age 26 (range 20–30) years with sphincter rupture during childbirth were followed at regular intervals for 1-year post partum. Thirty-four patients were primiparous and four multiparous. None of the latter had had traumatic childbirth before sphincter rupture. Nineteen patients had complete rupture of the anal sphincter, 14 had a deep partial rupture and five a superficial rupture only. The immediate repair of the sphincter was performed with 3/0 polyglycolic acid mattress sutures, the procedure being performed by a specialist in obstetrics.

At 3–5 days after delivery, anal manometry and electromyography were performed and the examinations repeated at 3, 6 and 12 months post partum. Nineteen patients did not complete all examinations because they were operated on for incontinence or because they were continent and did not want further investigation. Information on continence 12 months after childbirth was collected by telephone interview in these cases.

For comparison, 24 primiparous control subjects, median age 26 (range 21–32) years, who delivered mature infants vaginally were examined 3–5 days and 3 months after delivery. No control subject had had vacuum extraction or forceps delivery.

Sixteen women of median age 36 (range 24–49) years who were either nulliparous or had given birth atraumatically more than 2 years previously served as further controls.

The study was approved by the ethical committee of Copenhagen County.

Anal manometry

Investigations were performed with subjects in the left lateral position with hips and knees flexed. Maximum resting and squeeze pressures were measured with a low-compliance open-ended perfused polyvinyl catheter connected to a pressure transducer; results were displayed on a chart recorder[2].

Anal electromyography

With subjects in the left lateral position a disposable sponge electrode (Dantec 13L81, Skovlunde, Denmark) was placed in the anal canal with the pick-up plates at 3 and 9 o'clock. The electrode was lubricated in gel to secure contact with the anal mucosa. The electromyographic (EMG) signals were recorded on a Neuromatic 2000 M/C EMG recorder (Dantec) with filter settings at 10 Hz to 2 kHz. A ground electrode was placed on the left thigh. The maximum amplitude of an unbroken sharp wave at rest and during a voluntary squeeze was measured[3].

Statistical analysis

One-way analysis of variance was used for comparing differences between all groups. The two-sample t test and χ^2 analysis were used for comparison between groups.

Results

Thirty-four of the patients were primiparous. The maternity unit of Glostrup Hospital had a total of 2040 vaginal deliveries (singletons) in 1988, of which 1036 (51 per cent) were first children. The 95 per cent confidence interval (c.i.) of the difference in the rate of primiparity in patients with sphincter rupture compared with the rate of primiparity in the year 1988 was 29·5–49·5 per cent.

In 15 patients, vacuum extraction of the infant was performed, compared with an overall frequency of 15·9 per cent

Table 1 *History of deliveries in patients and primiparous controls*

	Patients ($n = 38$)		Primiparous controls ($n = 24$)	
Age (years)	26·3	(17·5–35·1)	26·1	(18·2–34·1)
Birth-weight (g)	3640	(2679–4602)	3559	(2426–4692)
Gestational age (weeks)	40·4	(38·2–42·6)	39·4	(37·1–41·6)
First stage of labour (h)	9·6	(−1·0 to 20·2)	8·6	(0·8–16·5)
Second stage of labour (min)	47·8	(−9·7 to 105·4)	38·5	(−7·4 to 84·4)
Head circumference (cm)	36·0	(32·9–39·1)	35·2	(32·5–37·9)

Values are mean (95 per cent confidence interval). None of the differences was significant (two-sample t test)

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in vaginal deliveries (95 per cent c.i. of difference 7·9–39·3 per cent). No forceps deliveries were performed.

Mediolateral episiotomy was performed in 32 of the 38 patients compared with six of the 24 primiparous controls (95 per cent c.i. of difference 38·4–80·1 per cent). The difference was still significant when patients with vacuum extraction were excluded (95 per cent c.i. of difference 24·0–73·9 per cent). No difference in birth-weight, gestational age, head circumference or the length of first or second stage of labour was found (*Table 1*).

Fourteen women were incontinent at follow-up (nine to solid or liquid faeces, five to flatus). Nine patients were incontinent 3 months after delivery and at 12 months five remained so. Seven of the patients who had had vacuum extraction and seven of the remaining 23 developed incontinence; this difference was not significant. *Table 2* shows symptoms in relation to the degree of rupture. No difference was found between continent and incontinent patients ($\chi^2 = 1{\cdot}93$, 2 d.f., $P = 0{\cdot}38$).

None of the control subjects had experienced faecal incontinence or incontinence to flatus. One-way analysis of variance of the manometric data and EMG findings showed a significant difference between incontinent patients, continent patients, primiparous control subjects and nulliparous control

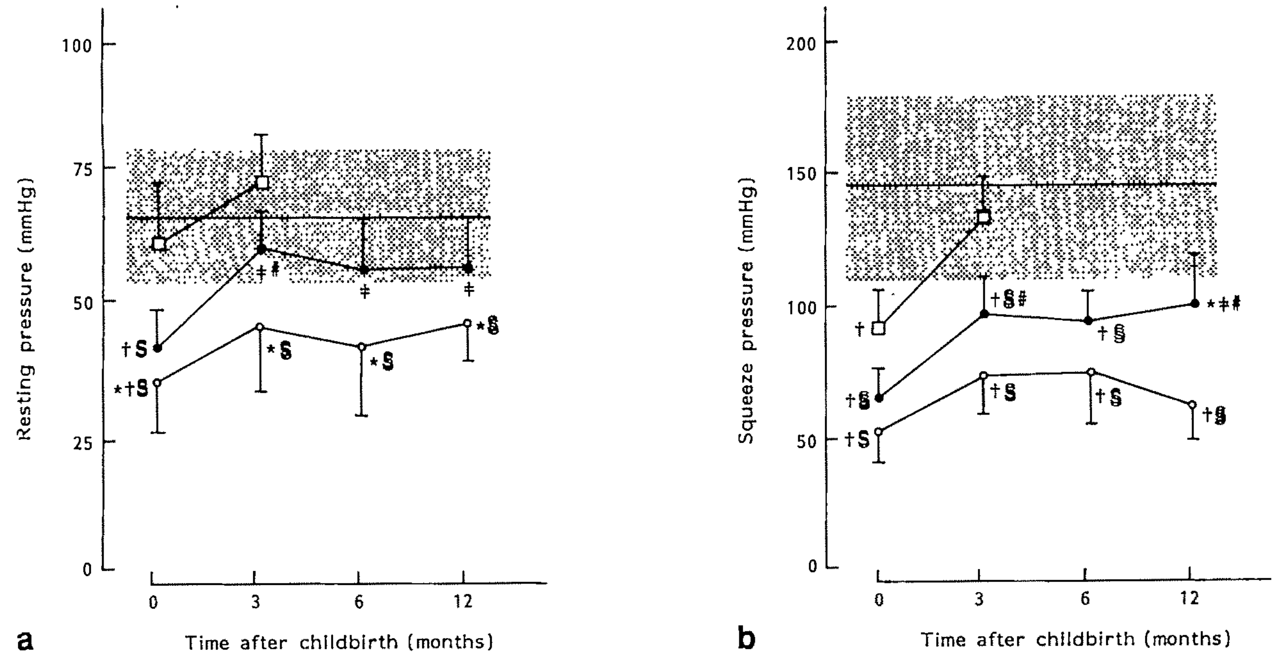

Figure 1 *Results of anal manometry:* **a** *resting pressure;* **b** *squeeze pressure.* o, *Incontinent patients* (n = *11 at 6 months;* n = *8 at 12 months);* ●, *continent patients* (n = *20 at 6 months;* n = *11 at 12 months);* ☐, *primiparous control subjects. Values are mean (95 per cent confidence interval).* ▨, *Mean (95 per cent confidence interval) for nulliparous controls.* *P < *0·05,* †P < *0·005* versus *nulliparous controls;* ‡P < *0·05,* §P < *0·005* versus *primiparous controls;* # P < *0·05 (incontinent* versus *continent patients); two-sample* t *test*

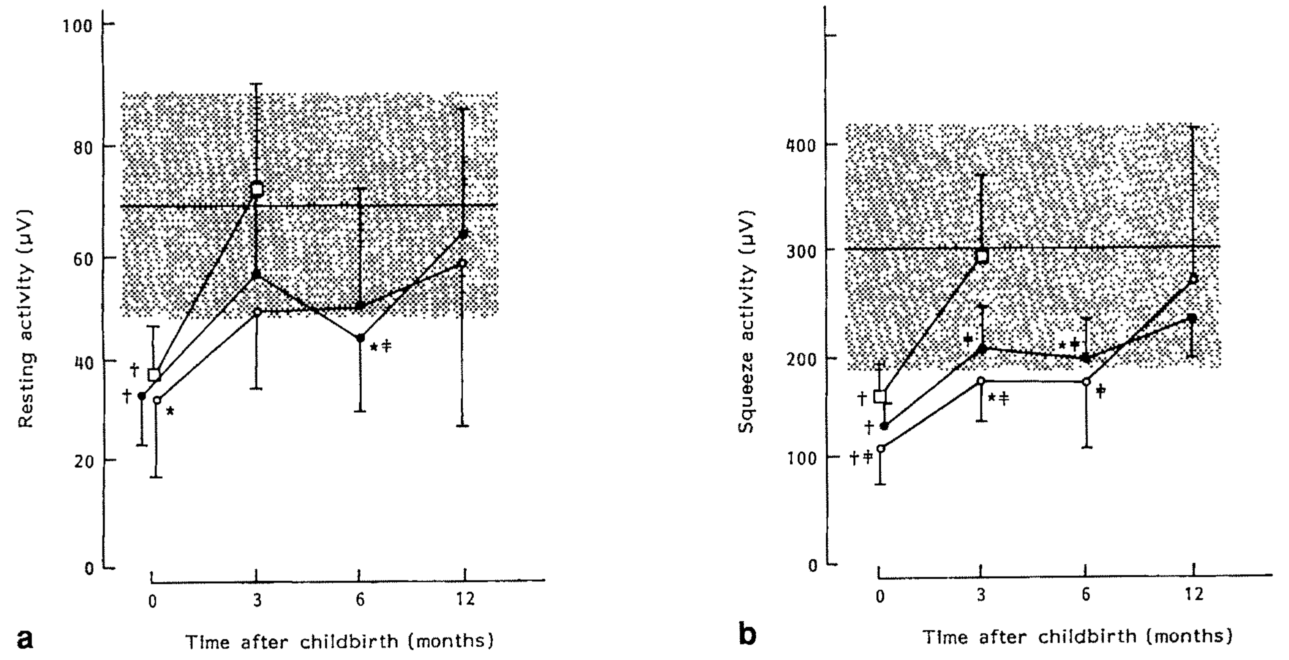

Figure 2 *Results of anal electromyography:* **a** *resting activity;* **b** *squeeze activity.* o, *Incontinent patients* (n = *11 at 6 months;* n = *8 at 12 months);* ●, *continent patients* (n = *20 at 6 months;* n = *11 at 12 months);* ☐, *primiparous control subjects. Values are mean (95 per cent confidence interval).* ▨, *Mean (95 per cent confidence interval) for nulliparous controls.* *P < *0·05,* †P < *0·005* versus *nulliparous controls;* ‡P < *0·05* versus *primiparous controls; two-sample* t *test*

Table 2 *Symptoms in relation to degree of sphincter rupture*

Rupture	No symptoms	Incontinence
Superficial	4	1
Partial*	10	4
Complete	10	9

*More than half of the sphincter involved. $\chi^2 = 1{\cdot}93$, 2 d.f., $P = 0{\cdot}38$

subjects ($P < 6 \times 10^{-9}$ for resting and squeeze pressure; $P < 0{\cdot}002$ for resting and squeeze EMG activity). The data were further analysed at 0, 3, 6 and 12 months.

Primiparous controls had decreased squeeze pressure compared with nulliparous controls ($P < 0{\cdot}005$) as well as decreased squeeze EMG activity ($P < 0{\cdot}005$) on the first days after delivery. At 3 months no difference from nulliparous controls was found. The incontinent patients had decreased resting and squeeze pressures at 0, 3, 6 and 12 months compared with both primiparous and nulliparous controls ($P < 0{\cdot}05$). Patients with sphincter rupture and preserved continence had decreased resting and squeeze pressures compared with primiparous controls ($P < 0{\cdot}05$), whereas only squeeze pressure was decreased compared with nulliparous controls ($P < 0{\cdot}05$); resting pressure was decreased compared with nulliparous controls only in the first 5 days after delivery. The manometric findings are shown in *Figure 1*.

Anal electromyography showed only a transient difference between primiparous and nulliparous control subjects on the first days after delivery. At 3 months no difference was found. In both incontinent and continent patients with sphincter rupture, resting anal EMG was decreased on the first days after childbirth when compared with nulliparous control subjects. At 3, 6 and 12 months no significant differences from either nulliparous or primiparous controls were found, except for continent patients at 6 months who had decreased activity compared with both control groups. During squeeze, anal EMG activity was decreased for both incontinent and continent patients with sphincter rupture at 3 and 6 months compared with primiparous controls. On the first days after childbirth, only incontinent patients had decreased activity compared with primiparous controls. Compared with nulliparous control subjects, incontinent patients had decreased activity at 0 and 3 months, whereas continent patients had decreased activity at 0 and 6 months. At 12 months no significant differences were found. EMG findings are shown in *Figure 2*.

Discussion

The results of this study show that incontinence to faeces and flatus is frequent in women with sphincter rupture during childbirth. Anal sphincter rupture was more frequent in the primiparous women and following vacuum extraction, confirming previous findings[1,4] where anal incontinence was present in 32 and 40 per cent respectively.

Episiotomy is suggested as a risk factor[4,5] and in the present study was performed more frequently in the patients than in the primiparous controls, supporting these suggestions.

The manometric studies showed a marked decrease of anal sphincter function at rest and during squeeze in the first days after delivery both in patients with sphincter rupture and primiparous controls. At 3 months after delivery both primiparous controls and continent patients had normal resting pressure compared with nulliparous control subjects. Resting pressure was reduced in incontinent patients, suggesting involvement of the internal anal sphincter as well since this sphincter is responsible for up to 70 per cent of the resting pressure[6]. In two of five patients who had a sphincter repair, internal sphincter damage was demonstrated. The squeeze pressure was persistently reduced in patients with sphincter rupture and most pronounced in incontinent patients. Pudendal nerve damage, which is likely to have occurred in a number of these patients, aggravates the condition and may prevent spontaneous recovery[7]. This subject is presently being investigated.

The difference in anal EMG between patients and control subjects was most pronounced for the incontinent patients, but not to the same extent as the manometric findings. In the incontinent patients only a minor part of the external anal sphincter muscle is lost. Since surface EMG represents a summation of action potentials[3], great alterations in the activity would not be expected. Mapping of the external anal sphincter with needle electrodes is used to demonstrate discontinuity of the sphincter[8]. In seven of eight of the incontinent patients in whom mapping was performed, a defect in the anterior part of the external anal sphincter between 10 and 2 o'clock was detected and would thus not interfere with the EMG recordings, whereas the manometric findings would be greatly affected. All five patients who underwent surgical repair became fully continent, proving that a sufficient amount of functioning anal sphincter muscle was still present.

Patients with sphincter rupture resulting from childbirth need careful follow-up. When faecal incontinence is present patients should be referred for surgical repair of the sphincter.

References

1. Haadem K, Ohrlander S, Lingman G. Long-term ailments due to anal sphincter rupture caused by delivery – a hidden problem. *Eur J Obstet Gynecol Reprod Biol* 1988; **27**: 27–32.
2. Petersen IK, Christiansen J. A study of the physiological variance in anal manometry. *Br J Surg* 1989; **76**: 69–70.
3. Sørensen M, Tetzschner T, Rasmussen OØ, Christiansen J. Relation between electromyography and anal manometry of the external anal sphincter. *Gut* 1991; **32**: 1031–4.
4. Sørensen SM, Bondesen H, Istre O, Vilman P. Perineal rupture following vaginal delivery. Long-term consequences. *Acta Obstet Gynecol Scand* 1988; **67**: 315–18.
5. Borgatta L, Piening SL, Cohen WR. Association of episiotomy and delivery position with deep perineal laceration during spontaneous delivery in nulliparous women. *Am J Obstet Gynecol* 1989; **160**: 294–7.
6. Lestar B, Penninckx F, Kerremans R. The composition of anal basal pressure. *Int J Colorectal Dis* 1989; **4**: 118–22.
7. Snooks SJ, Swash M, Setchell M, Henry MM. Injury to innervation of pelvic floor sphincter musculature in childbirth. *Lancet* 1984; **ii**: 546–50.
8. Petersen IK, Christiansen J. Traumatic anal incontinence: results of surgical repair. *Dis Colon Rectum* 1987; **30**: 189–91.

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Diaphragm-like strictures of the colon induced by non-steroidal anti-inflammatory drugs

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Diaphragm-like strictures of the terminal ileum have been described in association with non-steroidal anti-inflammatory drugs (NSAIDs)[1]. The first description of a patient with similar strictures in the colon is presented.

Case report

A 61-year-old woman presented with a 6-month history of intermittent colic, weight loss, diarrhoea and vomiting related to meals. She had a long history of osteoarthritis of the knees and lumbar spine, and had been treated with slow-release indomethacin for the previous 9 years.

On examination the patient was pale; the haemoglobin concentration was 8·5 g/dl and serum albumin level 26 g/l. Gastroscopy revealed both gastric and duodenal ulcers. The indomethacin was stopped and the patient treated with omeprazole and ferrous sulphate. Nevertheless symptoms persisted. A barium enema showed an unusual series of smooth contoured strictures in the proximal ascending colon (*Figure 1*).

At laparotomy the terminal ileum was found to be thickened and the ascending colon nodular; the serosa appeared unremarkable. A provisional diagnosis of Crohn's disease was made, and the terminal ileum and ascending colon were resected. Macroscopically the terminal ileum had a uniformly thickened wall and narrowed lumen. There were tight strictures with superficial ulceration both at the ileocaecal valve and in the ascending colon at 10 cm from the valve, with a few thin diaphragms in the caecum (*Figure 2*). Microscopically the prominent finding at sites of constriction in both the ileum and colon and at the diaphragms in the caecum was thickening of the bowel wall by submucosal fibrosis. The muscularis mucosa and muscularis propria showed focal fibrous replacement; the former had focal muscular hyperplasia. The serosa had mild fibrous thickening. There was some superficial mucosal ulceration with granulation tissue at the sites of constriction. The intact mucosa showed a moderate excess of chronic inflammatory cells with scanty focal lymphoid infiltrates through the bowel wall. No granulomas or definite evidence of Crohn's disease were seen. The lymph nodes showed follicular hyperplasia; the mesenteric vessels were unremarkable.

A diagnosis of diaphragm disease caused by NSAIDs was made after considering descriptions of similar lesions in the ileum[1].

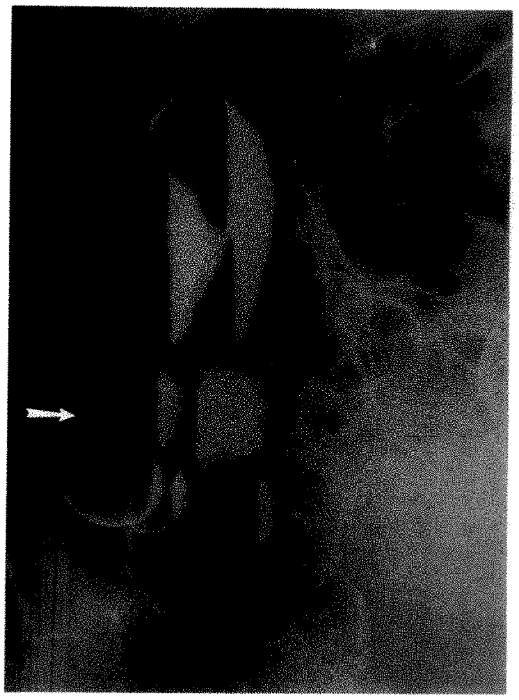

Figure 1 *Barium enema showing the stricture (arrow) in the ascending colon*

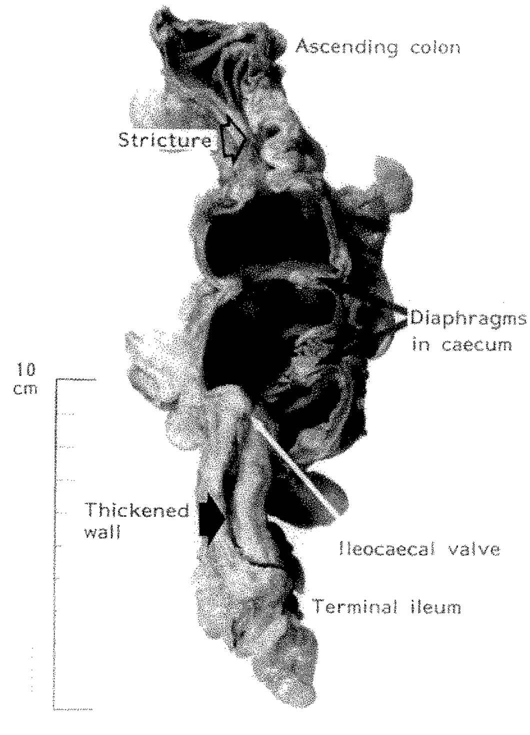

Figure 2 *Surgical specimen showing the terminal ileum with thickened wall, the narrowed ileocaecal valve, diaphragms in the caecum and stricture in the ascending colon*

Discussion

It is well recognized that NSAIDs can injure the stomach and duodenum. As early as 1966, caecal ulceration associated with indomethacin and oxyphenbutazone was reported[2]. Since then many other lower-tract complications of NSAID use have been described. Although colonic strictures in this setting have been mentioned previously[3], we believe this is the first description in a colectomy specimen of diaphragm-like strictures as detailed by Lang *et al.*[1] in the terminal ileum. The main histological feature is extensive submucosal fibrosis. The diaphragms, which resemble exaggerations of the plicae circulares, eventually progress to broad-based strictures[1]. NSAIDs appear to produce intestinal injury by inhibiting cyclo-oxygenase, thereby resulting in diminished levels of prostaglandins (particularly prostaglandin E) locally[4].

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Acknowledgements

The authors thank Dr I. Talbot for review of the pathology of this case.

References

1. Lang J, Price AB, Levi AJ, Burke M, Gumpel JM, Bjarnason I. Diaphragm disease: pathology of disease of the small intestine induced by non-steroidal anti-inflammatory drugs. *J Clin Pathol* 1988; **41**: 516–26.
2. Debenham GP. Ulcer of the cecum during oxyphenbutazone (Tanderil) therapy. *Can Med Assoc J* 1966; **94**: 1182–4.
3. Sheers R, Williams WR. NSAIDs and gut damage. *Lancet* 1989; **ii**: 1154 (Letter).
4. Bjarnason I, Peters TJ. Intestinal permeability, non-steroidal anti-inflammatory drug enteropathy and inflammatory bowel disease: an overview. *Gut* 1989; **30**(Spec): 22–8.

Paper accepted 30 July 1992

Errata

Derodra JK, Reidy JF, Jourdan MH. Embolization of superior haemorrhoidal artery in the management of life-threatening rectal bleeding. *Br J Surg* 1992; **79**: 704–5.

The October 1992 issue of the Journal contained an Erratum related to details of the main product used in the above Case Report. The company of Ferrosan has asked the Journal to clarify this point further. The product Spongostan is manufactured by Ferrosan A/S of Søborg, Denmark, and distributed in the UK by Johnson and Johnson Medical of Ascot, UK. This episode underscores to all those contributing to the Journal the need to provide accurate product information.

Kalra M, Beech MJ, Al-Khaffaf H, Charlesworth D. Autotransfusion in aortic surgery: the Haemocell System 350 cell saver. *Br J Surg* 1993; **80**: 32–5.

The Contents page entry for the above paper from the January 1993 issue lists the product in the title incorrectly. The Journal apologizes to the authors and especially to the manufacturers, Haemocell of Abingdon, UK.

SURGERY ABSTRACTS

Br. J. Surg. 1993, Vol. 80, March,
397–398

A selection of abstracts from February's issue of the journal.

Characterization of cholecystokinin receptors on the human gallbladder

Yukihiko Tokunaga, MD, Kenneth L. Cox, MD, Robert Coleman, BS, Waldo Concepcion, MD, Paul Nakazato, MD, *and* **Carlos O. Esquivel, MD, PhD,** *San Francisco, Calif.*

Background. *Several studies examined in vivo and in vitro biologic activity of the human gallbladder in response to cholecystokinin (CCK). However, few studies have demonstrated directly the interaction of CCK with receptors on the human gallbladder, which is responsible for this biologic activity.*
Methods. *To characterize CCK receptors on human gallbladder tissue, gallbladders were removed from human donor grafts that were being used for liver transplantation. The gallbladders were rapidly frozen and sectioned for measurement of binding of* ^{125}*I-Bolton-Hunter–labeled-CCK-8 and were cut into strips for in vitro bioassay.*
Results. *Binding of* ^{125}*I-BH-CCK-8 to human gallbladder was saturable, specific, and dependent on time, pH, and temperature. The binding was inhibited only by cholecystokinin-related peptides including CCK-8 (*IC_{50} *10 ± 1.0 nmol/L) (mean ± SD), des(*SO_3*)CCK-8 (*IC_{50} *0.9 ± 0.2 µmol/L), and gastrin-17-I (*IC_{50} *9.0 ± 2.0 µmol/L) or specific CCK receptor antagonist L-364,718. Computer analysis of binding of* ^{125}*I-BH-CCK-8 to gallbladder tissue showed a single class of binding sites with high affinity for CCK-8. Autoradiography localized binding of* ^{125}*I-BH-CCK-8 only to the smooth muscle layer of the gallbladder. In the bioassay des(*SO_3*)CCK-8 (*EC_{50} *1.2 ± 0.7 µmol/L) and gastrin-17-I (*EC_{50} *4.5 ± 2.4 µmol/L) were 150- and 563-fold less potent than CCK-8 (*EC_{50} *8.0 ± 2.2 nmol/L). The relative potencies of CCK agonists for inhibiting binding of* ^{125}*I-BH-CCK-8 agreed closely with their relative potencies for causing gallbladder contraction. The dose-response curve for CCK-8 alone to induce gallbladder contraction was not significantly different from those caused by CCK-8 plus 1 µmol/L tetrodotoxin or 1 µmol/L atropine.*
Conclusions. *These results characterized the CCK receptors on smooth muscle of human gallbladder as sulfate dependent and causing gallbladder contraction.* (SURGERY *1993;113:155-62.)*

Tumor necrosis factor-α inhibits in vivo collagen synthesis

Mark C. Regan, MB, BCh, FRCSI, Stephen J. Kirk, MB, BCh, FRCSI, Moira Hurson, BSc, Motohide Sodeyama, MD, Hannah L. Wasserkrug, BA, *and* **Adrian Barbul, MD, FACS,** *Baltimore, Md.*

In this study we sought to determine the in vivo role of tumor necrosis factor-α (TNF-α) at the wound-healing site. In vivo abrogation of endogenous TNF-α activity in experimental wounds by administration of anti-murine TNF-α rabbit serum resulted in a significant 77.5% increase in wound collagen deposition, as assessed by wound sponge granuloma hydroxyproline content. Administration of pharmacologic doses of recombinant murine TNF-α into subcutaneously inserted polyvinyl alcohol sponges resulted in an increase in collagen deposition (1594 ± 117 vs 1014 ± 49 and 1588 ± 135 vs 1014 ± 49 µg/100 mg sponge, for TNF-α in situ administration at a dose of 0.05 and 0.5 µg, respectively). This effect could be abolished by the simultaneous systemic treatment of the animals with the antiinflammatory drug indomethacin. The data suggest that the enhanced collagen deposition after TNF-α administration is a consequence of a nonspecific inflammatory activity that indirectly promotes collagen synthesis. The data also support the hypothesis that endogenous wound TNF-α down-regulates collagen synthesis during normal wound healing. (SURGERY *1993;113:173-7.)*

The role of eosinophils in interleukin-2/lymphokine-activated killer cell therapy

Toshiyuki Ishimitsu, MD, *and* **Motomichi Torisu, MD,** *Fukuoka, Japan*

When interleukin-2 alone or in combination with lymphokine-activated killer (LAK) cells is administered to patients with cancer, peripheral or local eosinophilia is frequently seen. To evaluate the role of eosinophils in this setting, we studied the functional changes of human eosinophils induced by the supernatant of LAK cell cultures. The chemotactic activity, change in chemiluminescence, superoxide production, expression of leukocyte integrins (CD11/CD18 family), and adherent activity to plastic dishes were investigated after stimulation of eosinophils with LAK cell culture supernatant. The chemotactic activity of eosinophils in the supernatant of LAK cell cultures was increased significantly, and this activity was chemotactic rather than chemokinetic by checkerboard analysis. Both chemiluminescence and superoxide production of stimulated eosinophils increased significantly compared with resting. In addition, eosinophil-adherent activity to plastic dishes was also increased. Among leukocyte integrins, CD11b expression on stimulated eosinophils increased. Moreover, eosinophil antibody-dependent cellular cytotoxity against Raji cells was enhanced after stimulation with the supernatant of LAK cell cultures. These results suggest that the eosinophils activated by LAK cells may play an important role in the antitumor effect of interleukin-2/LAK cell therapy. (SURGERY *1993;113:192-9.)*

Distribution of estrogen receptor in ductal carcinoma in situ of the breast

B. Chaudhuri, MD, K. A. Crist, PhD, S. Mucci, MD, M. Malafa, MD, *and* **P. K. Chaudhuri, MD,** *Toledo, Ohio*

Background. *Long-term antiestrogen therapy has been suggested as a possible treatment alternative for ductal carcinoma in situ (DCIS) of the breast. However, very little information is*

available on the distribution of estrogen receptor (ER) and treatment success with antiestrogen for such lesions.
Methods. *Thirty-two formalin-fixed tissue specimens of DCIS from 32 female patients aged 38 to 71 years were evaluated for the presence of ER by an immunoperoxidase technique. Antigenic sites for ER were exposed by treating the tissue sections with deoxyribonuclease followed by peroxidase-antiperoxidase staining with monoclonal antibody against ER. Parallel negative controls were run with negative control monoclonal antibody and normal rat serum. The quality control for positive staining was performed with tissue sections from specimens with known ER detected by the radioreceptor method.*
Results. *Eighteen (60%) of the 32 lesions were positive for ER. In 7 of the 18 lesions less than 25% of cells stained positive for ER and in 4 of the 18 more than 50% of cells stained positive for ER.*
Conclusions. *The incidence of ER in DCIS is similar to the incidence of ER in invasive carcinoma, leading to the speculation that ER-positive invasive carcinoma originates from an ER-positive precursor lesion. Because only 60% of the cases have detectable ER and approximately 70% of positively stained ERs are expected to be functional (as in invasive carcinoma), it appears that approximately 42% of the patient population with DCIS will benefit from antiestrogen therapy. (*SURGERY *1993;113:134-7.)*

Education about death and dying during the clinical years of medical school

William Rappaport, MD, *and* **Donald Witzke, PhD,** *Tucson, Ariz.*

Background. *Although there has been a dramatic increase in education about death and dying in medical school curricula, the physician's interaction with terminally ill patients and their families still causes concern. The purpose of our study was to determine the impact of the third-year clerkship on education of medical students about death and dying.*
Methods. *From August 1, 1988, to August 1, 1990, a questionnaire concerning the care of terminally ill patients was distributed to all students completing the third-year clinical clerkship at our medical school.*
Results. *One hundred and eighty questionnaires were distributed, of which 106 were returned, yielding a response rate of 59%. All students had cared for a terminally ill patient during their third year. Forty-four (41%) students responding had never been present when an attending physician talked with a dying patient, and 37 (35%) had never discussed with an attending physician how to deal with a terminally ill patient. During the surgical clerkship 77 (73%) students had never been present when a surgeon had to tell the family of a patient bad news after surgery, and 90 (85%) had never been present when an attending surgeon had informed a family that their relative had died. Despite the fact that the curriculum addresses the stages of death and dying, almost half of the students could not remember these. When they were discharging a terminally ill patient home, one third of students could not identify problems that would be encountered by the family in caring for the patient.*
Conclusions. *Fifty-seven (54%) felt that they were poorly equipped to deal with terminally ill patients on graduation from medical school, and 91% welcomed the opportunity to be educated in this area during the clinical years. (*SURGERY *1993;113:163-5.)*

Postoperative radiotherapy for carcinoma of the esophagus: A prospective, randomized controlled study

Manson Fok, FRCSEd, Jonathan S. T. Sham, DMRT, FRCCR, Damon Choy, DMRT, FRCR, Stephen W. K. Cheng, FRCSEd, *and* **John Wong, PhD, FRACS, FACS,** *Hong Kong*

Methods. *A prospective, randomized controlled study of radiotherapy after resection of esophageal carcinoma was carried out in 130 patients. Patients were stratified according to whether the resection was curative or palliative and were then randomized to receive postoperative radiotherapy or no additional treatment. Sixty patients underwent curative resection; 30 each were randomized into the radiotherapy group (CR+R) and the control group (CR). Seventy patients underwent palliative resection; 35 each were randomized into the radiotherapy group (PR+R) and the control group (PR).*
Results. *No complications occurred while the patients were undergoing radiotherapy treatment. On follow-up, complications in the intrathoracic stomach occurred in 24 patients (37%) who underwent radiotherapy compared with four patients (6%) in the control group ($p < 0.0001$). Seventeen of these 24 patients in the radiotherapy group had gastric ulceration and there were five deaths as a result of bleeding. Local recurrence developed significantly less frequently in the PR+R group compared with the PR group (seven patients [20%] vs 16 patients [46%]; $p = 0.04$); no difference was observed between CR+R and CR groups (10% and 13%, respectively.) Intrathoracic recurrence occurred in fewer patients in the radiotherapy groups (CR+R and PR+R) compared with the control groups (CR and PR) (four patients vs 15 patients; $p = 0.01$). In patients with residual tumor in the mediastinum after resection, two (7%) of 29 patients who underwent radiotherapy died of tracheobronchial obstruction, compared with nine (33%) of 27 patients in the control groups ($p = 0.03$). No difference in local recurrence was observed for extrathoracic or anastomotic recurrence. Distant metastasis developed in 12 patients (40%) in the CR+R group, nine patients (30%) in the CR group ($p = 0.59$), 24 patients (69%) in the PR+R group, and 18 patients (51%) in the PR group ($p = 0.22$). The time of onset of metastasis was 5.1 months for the PR+R group, which was shorter than the 8.5 months for the PR group ($p = 0.05$). The time of onset of metastasis was similar for the CR+R and CR groups (9.9 months and 11.0 months, respectively; $p = 0.76$). The overall median survival of patients after postoperative radiotherapy (CR+R and PR+R) was 8.7 months, which was shorter than the 15.2 months for the control groups (CR and PR) ($p = 0.02$).*
Conclusions. *The shorter survival of patients who underwent postoperative radiotherapy was the result of irradiation-related death and the early appearance of metastatic diseases. The role of postoperative radiotherapy is therefore limited to a specific group of patients with residual tumor in the mediastinum after operation, for whom radiotherapy can significantly reduce the incidence of local recurrence obstructing the tracheobronchial tree. (*SURGERY *1993;113:138-47.)*

Correspondence

Subtotal splenectomy in Gaucher's disease: towards a definition of critical splenic mass

Sir

We read with interest the Review by Drs Zer and Freud on subtotal splenectomy in Gaucher's disease (*Br J Surg* 1992; 79: 742–4). We fully agree with the sentiment that partial splenectomy may offer protection from overwhelming postsplenectomy sepsis and would seem a logical choice for use in children. However, in adults we question the logic of subtotal splenectomy specifically to delay the massive deposition of glucocerebroside in the liver and bone.

In 1980 a 21-year-old woman presented with chest pain, bone pain, anaemia and massive splenomegaly. A diagnosis of Gaucher's disease was made. At the age of 25 years the patient requested splenectomy because of massive abdominal distension. At laparotomy a grossly abnormal spleen weighing 4000 g was removed, histological examination of which confirmed typical advanced Gaucher's disease with little normal splenic parenchyma. Despite having evidence of liver and bone deposits of glucocerebroside, the patient remains well 8 years after splenectomy and is now pregnant for the second time. There has been no evidence of any rapid progression of liver or bone disease during that period. Accurate evidence is not available from the literature on the risks of accelerated deposition of glucocerebrosides, and because of this lack of knowledge we believe that, for adults, total splenectomy remains a useful therapeutic manoeuvre.

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Laparoscopic *versus* open appendicectomy: a prospective evaluation

Sir

We read the article by Mr McAnena and colleagues (*Br J Surg* 1992; 79: 818–20) and agree that laparoscopy and laparoscopic appendicectomy have a role in the management of patients with a clinical diagnosis of appendicitis. Laparoscopy confirms the diagnosis of appendicitis and also allows an inspection of other intra-abdominal and pelvic organs that would be impossible through a conventional gridiron incision.

However, our own early experience leads us to believe that the hospital stay after appendicectomy for acute appendicitis is not shorter after laparoscopic surgery. We believe that the systemic illness associated with appendicitis, not the surgical wound, delays the patient's discharge. Over a 4-month period, 23 patients with a clinical diagnosis of appendicitis have undergone laparoscopy: 16 had appendicitis, two had salpingitis and five had no obvious pathology. It is our policy, as with open exploration, to remove the appendix irrespective of its macroscopic appearance. Laparoscopic appendicectomy was successfully performed in 21 patients and two attempts were converted to an open procedure: in one case the appendicular ligature slipped and in one the appendix was retrocaecal. All patients without obvious pathology were discharged within 48 h. The mean stay for the remaining 18 patients, including the two who underwent open operation, was 4·3 (range 2–8) days. It would be interesting to know whether Mr McAnena and colleagues compared the laparoscopic and open procedure for patients who had a confirmed diagnosis of acute appendicitis, i.e. excluding those with a normal appendix.

We have no data, but it is our impression that patients suffer less pain after laparoscopic surgery. However, it would appear from the article that the wounds of the patients who had laparoscopic surgery were infiltrated with bupivacaine and the wounds of those who had a gridiron incision were not. We wonder whether this alone explains the difference in requirements for intramuscular analgesia between the two groups.

We would agree with the authors that a larger randomized trial is needed to resolve a number of issues. They state that in their study formal randomization was precluded on occasions by instrument availability. We are interested to know, on those occasions when randomization was possible, whether informed consent was obtained. We have been unable to conduct a randomized prospective study with informed consent as patients demand the minimally invasive procedure. We suspect that the randomized studies required will never be undertaken.

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Authors' reply

Sir

In response to the queries, patients who had a confirmed diagnosis of acute appendicitis had a significantly shorter hospital stay comparing laparoscopic *versus* open appendicectomy. Second, it has not been our practice to infiltrate open appendicectomy wounds with bupivacaine, and this may indeed have some bearing on the decreased analgesia requirements for the laparoscopic group. Third, informed consent was obtained from patients in whom laparoscopic surgery was performed. In relation to the suspicion of Mr Choy and colleagues that the randomized studies required will never be undertaken, I would draw to their attention a recent prospective randomized trial of laparoscopic *versus* open appendicectomy[1], which produced results that were the virtual mirror image of those presented in our own paper.

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1. Attwood SEA, Hill ADK, Murphy PG, Thornton J, Stephens RB. A prospective randomized trial of laparoscopic *versus* open appendectomy. *Surgery* 1992; **112**: 497–501.

Managing swabs in the operating theatre: a new method

Sir

I was interested in the paper on managing swabs in the operating theatre (*Br J Surg* 1992; 79: 776–7) by Mr McCombe and colleagues. In 1988 I visited a hospital in Heidelberg, Germany. In the interests of reducing the personnel required to run an operating theatre, swab counts and needle counts had been completely abandoned. I do not know how widespread this practice is in Germany, but it seemed to me that the cost savings far outweighed the extra time needed to ensure that packs placed in the wound were properly tailed and to make a final check of the wound before closing.

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Role of sequential leucocyte counts and C-reactive protein measurements in acute appendicitis

Sir
We read with interest the paper by Mr Thompson and colleagues (*Br J Surg* 1992; 79: 822–4) describing the use of serial leucocyte counts as an adjunct to clinical assessment in the diagnosis of acute appendicitis. The test described (that of an increase in the total leucocyte count over a 4-h period) was shown to have a sensitivity of 92 per cent and a specificity of 100 per cent and was therefore claimed to fulfil the criteria for a diagnostic test that could prove useful in assessing patients with equivocal clinical findings.

Of more practical relevance, however, is the negative predictive value of the test, the proportion of patients with a negative test result who did not have appendicitis. Although it is not quoted in the text, we calculate this value to be only 78 per cent. Furthermore, as the authors mention, those false-negative results (patients incorrectly predicted not to have appendicitis) were in cases of a perforated appendix and thus represent the very patients one would not wish to miss. Although a rising leucocyte count may be useful in certain cases, we would advocate extreme caution before refuting the diagnosis of acute appendicitis on the basis of this test.

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Iliofemoral *versus* femorofemoral bypass: a 6-year audit

Sir
The retrospective study of Mr Ng and colleagues (*Br J Surg* 1991; 79: 1011–13) attempted to compare iliofemoral bypass with femorofemoral crossover grafting for the treatment of unilateral iliac artery occlusion. Unfortunately, the authors have not compared like with like. When unilateral iliac artery lesions cannot be treated by interventional radiology, the surgical options depend on the presence or absence of a patent stump of the ipsilateral common iliac artery and on the overall fitness of the patient for operation, rather than on the preference of the surgeon. The unilateral procedure should be chosen whenever possible because it gives better haemodynamic results[1] with less risk of donor limb steal syndrome[2].

When no stump of the common iliac artery exists, the options are limited to a unilateral aortofemoral graft or a crossover procedure. The crossover option is attractive because it is a relatively minor operation with few side-effects. The question should then be whether taking the donor limb off the contralateral iliac artery[3] is superior to femorofemoral crossover. Using the larger iliac artery should provide better haemodynamics, and the suprainguinal incision causes less disturbance of local lymphatics with better healing[4]. With this procedure the contralateral groin is left undisturbed for future radiological or surgical interventional procedures.

The whole question of unilateral *versus* crossover procedures is in any case likely to become increasingly irrelevant with the advent of intraluminal stents for iliac occlusive disease.

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1. Lee RE, Baird RN. A haemodynamic evaluation of the femorofemoral crossover bypass. *Eur J Vasc Surg* 1990; 4: 167–72.
2. Nicholson ML, Beard JD, Horrocks M. Intraoperative inflow resistance measurement and predictor of steal syndromes following femoro-femoral bypass grafting. *Br J Surg* 1988; 75: 1064–6.
3. Baker R, Parker JC. Femorofemoral crossover grafts. *Br J Surg* 1972; 59: 701–4.
4. Hannafi M, McLoughlin GA. Comparison of iliofemoral and femorofemoral crossover bypass in the treatment of unilateral iliac artery occlusive disease. *Br J Surg* 1991; 78: 101–2.

Perineal trauma from cassette tape boxes

Sir
The recent Case Report by Mr Reyes and colleagues (*Br J Surg* 1992; 79: 1102) warns of the risk of perineal trauma from fragments of plastic cassette storage boxes. The paper raises a number of important points in the preparation of such reports.

First, the paper suggests that all three occupants of the car suffered similar injuries. It would appear from the text that only one of the victims (patient 2) was found to have a piece of plastic in the wound. To suggest that the other two injuries were caused in a similar way is conjecture. Second, patient 2 apparently had the foreign body removed from a deep perineal wound at the scene of the accident by a member of the fire service. Such intervention by members of the emergency services should be discouraged in the strongest terms. The unnecessary removal of foreign bodies in an uncontrolled manner from victims of multiple trauma may cause considerable morbidity and mortality. No comment is made on this point. Third, the occupants of the car are reported to have experienced 'a 160-m.p.h. deceleration'. As 'miles per hour' (m.p.h.) is a unit of velocity (*sic*) and not of acceleration, this statement is meaningless. Perhaps it would have been better phrased as 'a deceleration from 160 m.p.h.'.

Survival for all the occupants of a car travelling in excess of 160 m.p.h. colliding with a stationary vehicle would be worthy of report in its own right. I suspect that the authors are in fact reporting a collision of two vehicles with a combined impact speed in excess of 160 m.p.h. This being the case, each vehicle would have decelerated from a speed of less than 160 m.p.h.

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Authors' reply

Sir
We thank Mr Miles for his criticisms of our paper. The first point he makes suggests that absolute proof of the origin of these interesting perineal injuries was found in only one of the three cases. After an exhaustive search, including obtaining the opinion of police forensic experts, no other cause was found. We therefore concluded that it was likely that the injuries were from the same cause. It is up to readers to decide whether or not they feel that this is reasonable.

We agree that the unnecessary removal of foreign bodies in an uncontrolled manner may be undesirable but would point out that we were not at the scene of the accident when it occurred in the early hours of the morning. Officers in the emergency services have to make on-the-spot decisions as to whether the moving and transfer of injured victims to hospital with sharp penetrating perineal fragments would place them at risk of more serious injuries during the transfer as against the risk of serious haemorrhage if the sharp object were to be withdrawn.

We accept his comments on units but point out that implied in the phrase 'a 160-m.p.h. deceleration' is that it was from 160 m.p.h. to rest. This is an accepted terminology for head-on collisions, in which it is customary to add the closing speeds of the two vehicles together. In this case it is estimated that one vehicle was travelling at approximately 90 m.p.h. and the other at 70 m.p.h. It is undeniable that in each case there was a rapid deceleration.

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Quality of life following surgery for abdominal aortic aneurysm

Sir

The paper by Mr Magee and colleagues (*Br J Surg* 1992; 79: 1014–16) studying life quality in survivors of elective abdominal aortic aneurysm (AAA) surgery is welcome. That this quality appears to equal or even exceed preoperative levels is noteworthy, as this conclusion differs from earlier opinion[1]. However, the fact that patients were asked to recall details of well-being from up to 42 months before operation rather weakens the reliability of the study. Were the patients interviewed by the authors or independent interviewers? Were the patients told that the results would be analysed anonymously? Many patients are so willing to please. The more potential biases that could be excluded, the more convincing the results would be. Nevertheless, that so many patients perceived themselves as having relatively good life quality after aneurysm surgery is good news.

The results presented in the paper should not be used in isolation to support the need for a national aneurysm screening programme. The 8 per cent mortality rate of elective operation is a reminder that aneurysm repair can be a hazardous procedure. It would have been helpful in assessing this study to know the criteria on which elective operation was offered, the number of patients considered unfit for operation and the conditions from which they suffered. Many currently conclude that a national screening programme for AAA is not yet warranted[2–5].

At first glance, the reported decrease in postoperative sexual potency seems interesting. On closer inspection the results are even more intriguing because it appears that Bristol and Exeter men are unusually virile. From the data presented it can be calculated that the approximate mean age of the 120 male interviewees with aneurysm was 73 years. Some 119 of them are reported to have had 'normal sexual function' before operation. Considering their advanced years, perhaps the men of Bristol and Exeter were not only willing to please but also exceptionally able so to do.

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1. van Ramshorst B, van der Griend R, Eikelboom BC. Survival and life quality after surgery for ruptured abdominal aortic aneurysm. In: Greenhalgh RM, Mannick JA, Powell JT, eds. *The Cause and Management of Aneurysms.* London: WB Saunders, 1990: 433–40.
2. Canadian Task Force on the Periodic Health Examination. Special Article. Periodic health examination, 1991 update: 5. Screening for abdominal aortic aneurysm. *Can Med Assoc J* 1991; 145: 783–9.
3. Fowkes FGR, Ruckley CV, Powell JT, Greenhalgh RM. Screening for abdominal aortic aneurysms. *BMJ* 1992; 305: 1013 (Letter).
4. Mason JM, Wakeman A, Griffiths RK. Screening for abdominal aortic aneurysms. *BMJ* 1993; 305: 1013 (Letter).
5. Rose JS. Screening for abdominal aortic aneurysms. *BMJ* 1992; 305: 1014 (Letter).

Authors' reply

Sir

We are grateful for Dr Rose's comments. All patients were interviewed by the authors, but no knowledge of the type of operation or its indications was available at the time of questioning. The interviewees were indeed aware that the data were to be analysed anonymously. At the conclusion of the paper we did not advocate that our results be used in isolation to support the need for aneurysm screening but stated merely that they 'augment the argument for screening'. The debate on the necessity for a national screening programme continues.

We do not apologize for the virility of the Exeter and Bristol men, but are sorry if those in Hampshire cannot match this performance.

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Intraoperative balloon angioplasty

Sir

We read with interest the Leading Article on intraoperative angioplasty by Mr McCollum and colleagues (*Br J Surg* 1992; 79: 1125–6). We agree that intraoperative balloon angioplasty has a role and have practised this for some time. Like Mr McCollum and coauthors, our indications are an unexpected pressure drop at the groin, the treatment of inaccessible distal disease during the insertion of a femoropopliteal graft, and when a stenosis is demonstrated during embolectomy.

The important question is: 'Who should perform these intraoperative procedures?' We suggest that intraoperative angioplasty is normally the province of an experienced vascular radiologist, because: (1) it is a technique that requires training and practice to maintain a satisfactory level of skill; (2) it is technically more difficult in an operating theatre where viewing conditions are poor because of high ambient lighting; and (3) the relative immobility of theatre screening equipment makes it difficult to check the position of wires and balloons during the procedure. Thus the 'feel' of the wires and balloons during angioplasty becomes even more important, and this requires experience. Clearly there is an onus on radiologists in this field to make themselves available both in and out of hours, as do vascular surgeons. In our unit all four radiologists are capable of performing intraoperative angioplasty and two have a special interest in this procedure, thus enabling cover for holidays, sickness and so forth.

The most important aspect is that vascular radiologists and surgeons continue to work together for the benefit of the patient rather than see each other as a threat to their future existence.

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Reperfusion injury in skeletal muscle: a prospective study in patients with acute limb ischaemia and claudicants treated by revascularization

Sir

I read with interest the recent paper by Mr Adiseshiah and Drs Round and Jones (*Br J Surg* 1992; 79: 1026–9). The authors are to be congratulated for their thorough investigation of this difficult clinical problem. I am, however, concerned that insufficient evidence is presented to support the hypothesis that the observed changes in skeletal muscle were primarily the result of reperfusion injury. Group 2 patients (with claudication) cannot be used as a control for observations made in group 1 (acute ischaemia). The difference between the groups is not limited to the presence or absence of complete ischaemia. Thus it is not valid to assume that the different observations in each group were all related to revascularization. The changes in skeletal muscle may have occurred during ischaemia but become detectable only at a later stage. No data are presented on histological analysis of skeletal muscle subject to prolonged ischaemia without revascularization.

Oxygen free radicals have been implicated in reperfusion injury but are difficult to assay directly. Research on reperfusion injury has often used the action of oxygen radical scavengers as an indirect bioassay to detect reperfusion injury. The results presented by the authors provide valuable information on the evolution of skeletal muscle damage after revascularization but fail to provide conclusive evidence that the biochemical and histological changes observed result from oxygen radical formation and reperfusion injury. This is an acceptable hypothesis but remains unproven. As such, the title of the paper is misleading.

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Authors' reply

Sir

We thank Mr Moran for his interest in our study and found his observations stimulating. He points out that the damage may not have arisen solely from reperfusion and that some change may have occurred while the muscle was ischaemic. The fact that the histological appearance of the muscle in the group 1 patients was initially normal and that there was a delay of around 24 h between the operation and the release of creatine kinase indicates that the damage evolves slowly. We believe that there are changes occurring in muscle kept ischaemic for several hours that result in necrosis seen a day or so after the circulation is restored. If at the end of the salvage operation the muscle had appeared necrotic and large amounts of soluble protein had been released immediately into the circulation, we would have assumed that the damage was a direct consequence of ischaemia. The fact that this was not the case raises the possibility that there is some interaction between the returning blood and the metabolically depleted muscle. The nature of any such interaction is clearly open to speculation, and the observations presented do not provide any evidence as to whether free radicals are involved.

The reason claudicants were used as a control group for comparison was twofold. First, although they did not suffer the preoperative ischaemia experienced by the patients with acute ischaemia, both groups did undergo intraoperative ischaemia caused by arterial clamping. We wished to look at intraoperative clamping in case it contributed in any way to rhabdomyolysis. Second, we were curious to know whether there was evidence of rhabdomyolysis at all in claudicants during and after reconstruction. We do not suggest, and there is no such evidence, that claudicants suffer the histological changes that we observed in patients with acute ischaemia.

We feel that Mr Moran is a little hard in suggesting that the title of our paper was misleading. We do not imply any mechanism by use of the term 'reperfusion injury', rather we are simply using a recognized phrase to indicate that the topic of the paper was the injury that often occurs after successful revascularization in cases of acute muscle ischaemia.

Finally, we agree that the role of oxygen free radicals in reperfusion injury is unclear, and at present these are best regarded as an index of damage rather than as a cause of it. We never proposed the latter concept.

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Physiological and metabolic responses to open and laparoscopic cholecystectomy

Sir

We read with interest the study of Mr Mealy and colleagues (*Br J Surg* 1992; 79: 1061–4) comparing the physiological and metabolic responses to open and laparoscopic cholecystectomy. We have compared similar parameters after minilaparotomy and laparoscopic cholecystectomy as part of a prospective randomized trial. In our study, laparoscopic cholecystectomy resulted in better postoperative pulmonary function and oxygen saturation, and lower pain scores and morphine consumption (using a patient-controlled analgesia device), than minilaparotomy cholecystectomy[1–3]. In these respects our findings are in agreement with those of Mealy *et al.*

By contrast, our findings on the metabolic response to surgery after the two procedures (ten patients in each group)[4] differ significantly from those of Mr Mealy and co-workers (*Table 1*).

There was a wide variation in the metabolic response within groups, but no significant difference between them. The C-reactive protein response after laparoscopic cholecystectomy in our study was more than twice that found by Mealy *et al.* Given that there is wide variation in the magnitude of the metabolic response to surgery, it is not surprising that studies with small patient numbers can produce such different results. In Mr Mealy's study, patients were not randomized. Patient selection bias may therefore account for the difference in findings.

Table 1 *Metabolic responses to cholecystectomy*

	Laparoscopic operation	Minilaparotomy	*P**
C-reactive protein at 48 h (mg/l)	118(50)	122(30)	0·11
Interleukin-6 at 24 h (pg/ml)	227(41)	252(46)	0·60

Values are mean(s.e.m.). *Mann–Whitney *U* test

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1. McMahon AJ, Baxter JN, Anderson JR *et al.* Assessment of pain after laparoscopic and minilap cholecystectomy: a randomized trial. *Br J Surg* 1992; **79**: 1224 (Abstract).
2. McMahon AJ, Baxter JN, Anderson JR *et al.* Pulmonary function after laparoscopic and minilap cholecystectomy: a randomized trial. *Br J Surg* 1992; **79**: 1226 (Abstract).
3. McMahon AJ, Baxter JN, Anderson JR *et al.* Post-operative pain and analgesia requirement after laparoscopic and minilap cholecystectomy: a prospective randomized trial. *Gut* 1992; **33**: S63 (Abstract).
4. McMahon AJ, O'Dwyer PJ, McMillan D *et al.* Does the laparoscopic method result in a reduced metabolic response to surgery? *Ir J Med Sci* 1992; **161**(Suppl 11): 39 (Abstract).

Authors' reply

Sir

We appreciate the interest shown by Mr McMahon and colleagues in our paper. There does indeed appear to be a discrepancy between the inflammatory response as measured by C-reactive protein (CRP) induced by laparoscopic surgery in our patients and their data. There are many reasons for this discrepancy. Differences in assay may be a factor. However, the wide variation in the magnitude of the metabolic response to surgery is important (as they state). In this regard, our data demonstrate acceptable variance or spread; in addition, the differences in CRP response in our study correlated with other parameters examined, in particular pain scores and respiratory responses. We note the wide variation in CRP levels in McMahon's patients, which may account for their difficulty in demonstrating differences between the two groups.

A further difficulty lies in the greatly raised interleukin (IL) 6 levels reported by Mr McMahon and colleagues. Although we have no direct comparison for our study, it is interesting to note that their IL-6 levels are approximately twice those seen following abdominal aortic aneurysm repair[1]. Undoubtedly anaesthetic and operative technique, sampling method and assay variability are of great importance in this regard.

We stand by our findings and feel that the wide variation in their results and their small numbers may account for the differences between the two sets of data.

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1. Baigrie RJ, Lamont PM, Kwiatkowski D, Dallman MJ, Morris PJ. Systemic cytokine response after major surgery. *Br J Surg* 1992; **79**: 757–60.

Place of routine operative cholangiography at cholecystectomy

Sir
In their recent article For Debate (*Br J Surg* 1992; **79**: 945–7), Messrs Corder, Scott and Johnson accurately represent the prevailing British view favouring the use of peroperative cholangiography during open cholecystectomy (quoting Cahill and Pain's survey of general surgeons[1]). If peroperative cholangiography is regarded as good practice during open operation, are there sufficient grounds to drop it selectively in the laparoscopic procedure? The authors point out that not all common bile duct (CBD) stones are predicted by patient history, biochemistry or ultrasonography but also state that 'cholangiography may be selectively omitted in the safe knowledge that symptomatic bile duct stones will not present subsequently'.

We have employed a policy of routine peroperative cholangiography, using image intensification, during our first 114 laparoscopic cholecystectomies for gallstones. Patients with jaundice or a dilated biliary tree underwent preoperative endoscopic retrograde cholangiopancreatography (ERCP). CBD stones were found in 18 of 114 patients (16 per cent): in five cases at preoperative ERCP and in 13 at peroperative cholangiography. CBD stones were confidently identified at peroperative cholangiography in eight patients in whom calculi were not predicted by history, biochemistry or ultrasonography. Subsequent ERCP 4–96 days after operation confirmed duct stones in two of eight patients, indicating spontaneous passage in the other six. We have therefore identified a low incidence (two of 89) of truly retained calculi in patients not suspected of harbouring duct stones. Whether any sequelae would arise from leaving such stones behind remains conjectural. We believe that both identification of the anatomy and development of cholangiographic skills are valid additional reasons for recommending peroperative cholangiography in all laparoscopic cholecystectomies.

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1. Cahill CJ, Pain JA. Current practice in biliary surgery. *Br J Surg* 1988; **75**: 1169–72.

Prospective randomized trial comparing the Shouldice technique and plication darn for inguinal hernia

Sir
I read with interest the prospective study by Mr Kingsnorth and colleagues (*Br J Surg* 1992; **79**: 1068–70) comparing the Shouldice repair and plication darn for inguinal hernia. The results of the study that they present do not support their view that the failure of the Shouldice technique among the junior surgeons was the result of inexperience with the operation compared with their experienced consultant colleague. Indeed, there is no significant difference using the χ^2 test in the overall recurrence rate of inguinal hernia repair performed by the consultant surgeon compared with the juniors. What is clear is that the recurrence rate after Shouldice repair in this study (seven of 144) is significantly worse ($P < 0.05$) than that reported in a series from a large British centre (seven of 780)[1,2].

The debate as to the best operation for inguinal hernia is steeped in surgical tradition. However, there is no doubt that the best results have been obtained by specialist surgeons working in specialist centres using the Shouldice technique[1,2]. Mr Kingsnorth's finding that this technique was no better than the plication darn should not be used as an excuse to advocate the latter, despite its apparent simplicity, speed and familiarity. On the contrary, I believe that it is time to aim for all inguinal hernias to be managed by specialist hernia surgeons. The experience of the Shouldice Clinic suggests that there is a long learning curve to the Shouldice technique[1], a point in favour of such a move. The emergence of various specialties, including vascular surgery, urology and, more recently, colorectal surgery, confirms that the myth of general surgery as a specialty has long been shattered. In order best to serve the interests of our patients further specialization is both desirable and inevitable.

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1. Devlin HB. *Management of Abdominal Hernias*. Butterworths, London: 1988.
2. Glassow F. Inguinal hernia repair using local anaesthesia. *Ann R Coll Surg Engl* 1984; **66**: 382–7.

Authors' reply

Sir
Mr Wyatt raises several issues, some specific to our paper and others more general relating to the overall management and treatment of inguinal hernia. There are two specific points raised concerning our data. First, he claims there is no significant difference in the overall recurrence rate of inguinal hernia repair performed by the consultant compared with the junior surgeons. In the paper, no breakdown was given of the recurrences except the statement that no surgeon was responsible for more than two. For this reason, and also because the 11 recurrences were shared by eight surgeons, no statistical comparison is possible. Second, there is the question of comparison with Devlin's series of 780 Shouldice repairs performed by a single surgeon over a 12-year period. The results of this series are considerably better, but our study was designed to address the question of the applicability of the specialist technique outside a specialist centre to surgeons in training.

Regarding the more general questions, we did not advocate plication darn as the operation of choice for inguinal hernia. The Shouldice repair must remain the 'gold standard'. With the advent of prosthetic material and laparoscopic repair, it is important that effective operations such as the Shouldice repair are not discarded before the new techniques have been well tested prospectively both by experts and master hernia surgeons and by general surgeons in district general hospitals. We strongly disagree that all inguinal hernias should be repaired in specialist centres, although the learning curve for the Shouldice operation may be as long as 1000 repairs, as pointed out in our paper. A case can be made for specialized ambulatory surgical centres or specialized hernia hospitals to serve a region or a larger population[1]. In fact, the first hernia centre (a private hospital) has been set up very successfully in London; the centre has advertised widely in the media and business is booming. A 'no-waiting list' daycase approach is being offered. As hernia surgery rises up the agenda with the advent of laparoscopic techniques, the National Health Service is seen to be dragging its feet owing to lack of funding. Regional hernia centres could fulfil a useful function by assisting in bringing down waiting lists, training surgeons in specialized techniques of herniorrhaphy and acting as a tertiary referral unit for complex cases. Clearly, British hernia surgery has much room for improvement with an overall recurrence rate of 10 per cent, patients waiting a mean of 60 days for operation and then spending a mean of 5 days in hospital. Some 40 000 trusses are prescribed per year, presumably by doctors who do not wish surgeons to treat their patients. Only 7 per cent of hernias are repaired as day cases, and the age-specific surgery rate in the UK is one-third that in the USA. We agree with the sentiments expressed in the recent editorial in the *American Journal of Surgery*[2]: improvements in treatment of inguinal hernia depend on standardization of preoperative, operative and postoperative management which simplifies the overall approach.

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1. Morgan M, Reynolds A, Swan AV, Beech R, Devlin HB. Are current techniques of inguinal hernia repair optimal? A survey in the United Kingdom. *Ann R Coll Surg Engl* 1991; **73**: 741–5.
2. Deysine M, Sorroff HS. Must we specialize herniorrhaphy for better results? *Am J Surg* 1990; **160**: 239–41.

Book reviews

Moving to Audit – An Educational Package for Hospital Doctors and General Practitioners

C. Arnold, J. Bain, R. A. Brown, R. M. Harden, J. M. Laidlaw, S. McAleer and R. A. Wood. 300 × 220 mm. Pp. 128. Illustrated. 1992. Dundee: Ninewells Hospital and Medical School Postgraduate Office. £29.

Having just completed a report on a recent hugely oversubscribed conference for audit personnel held at The Royal College of Surgeons of England, it was a little disheartening to look at the front cover of this excellent book and find the words 'What every doctor needs to know about medical audit'. This contradiction becomes increasingly reinforced with the book's strong emphasis on team work and the recognition that few audits fail to cross professional boundaries, whether they be clinical, administrative, scientific or managerial.

The *Resource Book* – perhaps '*Interactive Audit Primer*' would be more appropriate as the package contains many inserts, pockets and cards that encourage feedback by means of addressed response cards – makes full use of icons, cartoons and graphics to ease the reader through the various stages of audit. This it does by approaching the many phases and disciplines involved in an audit cycle in a chronological manner chapter by chapter and then elaborates with judicious use of the worked example.

The book is thoroughly up to date in the way it deals with the relationship between research and audit, the rigour required in audit methodology, and the realities of implementing change. This book arrives at a time when there is much interest and debate in these areas. It deals with both these and the fundamentals in a way which demystifies the audit process. It is particularly to be recommended because it aggressively dismisses the 'audit – yawn, yawn' philosophy, and presents audit as an indispensable and intellectually demanding activity for modern clinicians, audit personnel and managers.

M. Emberton

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UK

Low Molecular Weight Heparin

T. W. Barrowcliffe, E. A. Johnson and D. P. Thomas. 235 × 155 mm. Pp. 209. Illustrated. 1992. Chichester: John Wiley and Sons. £32·50.

Venous thromboembolism is the most common preventable cause of death in hospital patients, including those in surgical wards. In the past 20 years, randomized controlled trials have shown that standard unfractionated heparin is effective in both prophylaxis and treatment. However, there is room for improvement on standard heparin: it is an animal 'soup' of molecules of variable molecular weight, it requires intravenous infusion or multiple subcutaneous injection, and its antithrombotic efficacy is tempered by an increased risk of bleeding (including postoperative bleeding).

In the 1970s, Dr E. A. Johnson of the newly formed National Institute for Biological Standards and Control (NIBSC) in Hampstead was the first to fractionate heparin; with his clinical colleagues he discovered that the molecular weight of heparin was an important determinant of its biological properties. In this book, he and the current and former heads of the Division of Haematology of NIBSC (Drs Barrowcliffe and Thomas) chronicle the large number of biological and clinical studies of low molecular weight heparins performed in the past 15 years. Their useful exposition is clear, readable, well illustrated and comprehensively referenced up to 1991. They conclude that low molecular weight heparins have two advantages over standard heparin: they are effective as a single daily subcutaneous injection, and they have increased antithrombotic efficacy without an increased risk of bleeding. This book merits a place in all postgraduate libraries and is a useful reference for surgeons and anaesthetists, as well as physicians, haematologists and pharmacologists.

G. D. O. Lowe

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Endovascular Surgery. 2nd ed.

S. S. Ahn and W. S. Moore (eds). 286 × 222 mm. Pp. 592. Illustrated. 1992. Philadelphia, Pennsylvania: W. B. Saunders. US $135.

There are so many exciting new fields of research related to the treatment of vascular disease that one can almost understand the need for all 98 of this book's contributors. Mostly from the USA, they have provided no fewer than 64 chapters for this substantial volume.

The first large section is devoted to endovascular imaging; mainly this is angioscopy, but a couple of chapters on intravascular ultrasonography provide an appropriate balance. The section contains not only clinical indications and results, but also guidance on organizing an angioscopy programme, maintenance of equipment, and what one might expect of angioscopy in terms of efficacy and safety.

The second main section discusses balloon angioplasty and its chapters provide an excellent source of data on outcome as well as technique. Mechanical atherectomy and laser/thermal angioplasty are dealt with in the next sections; the presentations are both authoritative and exhaustive. The penultimate block of chapters deals with adjunctive procedures to endovascular surgery, including catheter thrombolysis and stenting. I felt that this section was rather shorter than its clinical implications would seem to merit but, to be fair to the editors, quite a bit of ground was covered, with even a chapter on endovascular grafting for aortic aneurysm. The book ends with chapters on biological effects of endovascular instrumentation with myointimal hyperplasia given due prominence.

This is a book for those interested in new developments in the rapidly changing field of vascular surgery. Most chapters are worthwhile reads for any vascular surgeon; many are exciting pointers to our vascular surgical future. The second edition of *Endovascular Surgery* comes only 4 years after the first – read it before it exceeds its shelf life.

J. A. Murie

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UK

Diagnostic Picture Tests in Clinical Surgery

W. F. Walker. 189 × 120 mm. Pp. 128. Illustrated. 1992. London: Wolfe. £7·95.

This small book of clinical pictures is one of several atlases produced by Professor W. F. Walker, recently retired as Professor of Surgery at the University of Dundee. The book is aimed at the surgeon in training and hopes to appeal to the 'general clinician'. In recent years an abundance of atlases have appeared in the medical press and opinion is often sharply divided on their value. I confess that I am one of those who feels that atlases of this type have great difficulty in making a real contribution to medical literature. This particular volume hopes to test the traditional skills of history taking in relation to clinical signs but, sadly, I fear it often fails. Although the quality of the individual photographs is usually good and the spectrum of material wide, it is difficult to deduce the answers to the sequential questions from the photograph alone. In many cases, even knowing the answer, one has difficulty in following the sequence of answers. Inevitably, there are one or two statements that many would consider inaccurate, not least that testicular descent into the scrotum takes place at 7 weeks of gestation. It is difficult to target this volume at a specific group of clinicians. It is the sort of book that one can enjoy flicking through to test one's clinical acumen, but I find it difficult to believe that many surgeons in training would wish to buy it. The book competes in a crowded market place where this technique has been widely employed by journals and specialist textbooks.

A. J. McKay

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Principles of Trauma Surgery

J. A. Moylan (ed.). 310 × 255 mm. Pp. 299. Illustrated. 1992. London: Gower Medical. £90.

Advances in prehospital care and triage, and the evolution of sophisticated trauma centres in response to major and life-threatening injuries, have stimulated a proliferation of pertinent books and publications. This large volume appears at the end of a decade of ever-sharpening focus on the proper management of surgical trauma. It contains 20 chapters, half of which are contributions from the editor and other surgeons from North Carolina, USA. Among them are chapters on the management of a comprehensive range of regional and specific organ injuries, but head and spinal injuries, with the exception of blunt neck trauma, appear to have been deliberately omitted. The book does not aim to offer the structured approach to the treatment of the multiply injured individual that one expects to find in some books on trauma; this is an observation and not a criticism of this excellent volume. Early in the text are contained detailed but clearly set out sections on the pathophysiological basis for the treatment of shock and the provision of respiratory support. Further helpful portions of the text cover mechanisms of pulmonary and cardiac injuries in a preamble to their recognition and management.

Each chapter sets out essential practical guidelines of diagnosis and management, along with operative techniques aimed at improving survival and quality of outcome. In dealing with abdominal trauma, injuries to solid organs, viscera, alimentary and genitourinary tracts are comprehensively represented but, significantly, those to the major vessel trunks in the abdomen appear to have been ignored. Against that, space is set aside for subjects such as hand injuries, burns and paediatric trauma, which are often omitted in other texts. Sections on nutritional support and critical care management are extremely helpful and instructive. The book is liberally interspersed with superb clear colour diagrams, algorithms and tables. This technique is also used to highlight key information or illustrate mechanisms of injury or operative manoeuvres. The attractive layout of the volume invites the reader to leaf through it and the book certainly ought to be on the shelves of any institution in which trauma care is taught or where victims of trauma receive treatment.

A. A. B. Barros D'Sa

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UK

Reoperative General Surgery

D. G. MacQuarrie and E. W. Humphrey. 220 × 285 mm. Pp. 833. Illustrated. 1992. St Louis, Missouri: Mosby–Year Book. £94.

Surgery, like marriage, is more difficult the second time round. This book, written by an impressive group of American doctors and one lawyer, attempts to provide guidelines for those of us (all of us) who are unlucky enough to have to reoperate on our patients. Although the emphasis of the book is on reoperation, there are excellent sections on diagnostic imaging and interventional techniques as well as endoscopy. The pathophysiology of wound healing and the problems of nutrition in a patient requiring further intervention are well covered and there is an extensive section about haemostasis in surgery.

The main sections of the book are devoted to reoperations on the gastrointestinal tract, thorax, abdomen, solid organs and soft tissues; endocrine disease is also covered. A section on medicolegal aspects of reoperation gives an insight into the mind of an American lawyer and how malpractice law operates in the USA. All of us would agree with the statement 'there can be little question that poorly kept hospital or office records are a guaranteed medico-legal hornets' nest'. The chapters in this book are well written, easy to read and well illustrated with photographs (some in colour) and line drawings. The text is well referenced and gives clear advice on the management of difficult problems. While the book is aimed at that elusive figure, the general surgeon, a small complaint would be that it ignores vascular surgery almost completely. There is nothing about venous ulceration or recurrent varicose veins and little on the management of iatrogenic vascular injury during reoperation.

It is appropriate that the editors have dedicated this book to C. S. Pierce, who was, like them, a US government employee. More importantly, however, he is recognized as a great proponent of pragmatism in surgery. A pragmatic approach is required when dealing with the patient who needs a second operation. This book succeeds in its attempt to provide informed guidelines for a most difficult area of surgery.

D. Bouchier-Hayes

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Ireland

Notices and announcements

29–30 March 1993
Thoracoscopic Surgery Course
Amsterdam, The Netherlands
Information: Factory/Congress Office, Bloemgracht 169, 1016 KN Amsterdam, The Netherlands

5 April 1993
Injury Research Group 1993 Meeting
Milton Keynes, UK
Information: Dr R. N. Barton, North-western Injury Research Centre, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

14–16 April 1993
Association of Surgeons of Great Britain and Ireland Annual Meeting
Birmingham, UK
Information: Caroline Ross, Association of Surgeons of Great Britain and Ireland, at The Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

18–22 April 1993
International Congress on Advances in Brain Revascularization
Eilat, Israel
Information: Orta Ltd, 2 Kaufman Street, PO Box 50 432, Tel-Aviv, Israel 61 500

5–7 May 1993
Angioscopy Symposium/Course
Amsterdam, The Netherlands
Information: Factory/Congress Office, Bloemgracht 169, 1016 KN Amsterdam, The Netherlands

18–20 May 1993
Laparoscopic Suturing and Stapling
Antalya, Turkey
Information: Factory/Congress Office, Bloemgracht 169, 1016 KN Amsterdam, The Netherlands

19–22 May 1993
Eighty-fourth Annual Meeting of the American Association for Cancer Research
Orlando, Florida, USA
Information: AACR Office, Public Ledger Building, 620 Chestnut Street, Suite 816, Philadelphia, Pennsylvania, USA

28 May 1993
Endovascular Procedures
Bournemouth, UK
Information: Mr S. Parvin, Department of Surgery, The Royal Bournemouth Hospital, Castle Lane East, Bournemouth, Dorset BH7 7DW, UK

3–5 June 1993
First European Congress of the European Association for Endoscopic Surgery
Cologne, Germany
Information: Medikon-Heide Harzheim, Irmtraud Surmann, PO Box 50 14 70, D-5000 Köln, Germany

7–8 June 1993
8th International Symposium – Applied Physiology in Clinical Respiratory Care
Rotterdam, The Netherlands
Information: Dr O. Prakash, Thorax Centre BD 164, Dijkzigt Hospital, Dr. Molewaterplein 40, 3015 Rotterdam, The Netherlands

8–11 June 1993
World Association of HPB Surgery 1st European Congress of Surgery
Paris, France
Information: EHPBS Congress Secretariat, Congress House, 65 West Drive, Cheam, Surrey SM2 7NB, UK

9–12 June 1993
The Endocrine Society 75th Annual Meeting
Las Vegas, Nevada, USA
Information: Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

4–9 July 1993
Endosurgery – the State of the Art
Hamilton Island, North Queensland, Australia
Information: Kathy Noble, Centre for the Study of Endosurgery, Department of Surgery, Alfred Hospital, Commercial Road, Prahran, Victoria 3181, Australia

5–8 July 1993
First International and Eighth European Conference on Clinical Hemorheology
Vienna, Austria
Information: Professor E. Ernst, Department of Physical and Medical Rehabilitation, University of Vienna, AKH Währinger Gürtel 18–20, 1097 Vienna, Austria

6 July 1993
Current Issues in Epidemiology: the Prevention and Control of Chronic Disease
Cambridge, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

6–17 July 1993
Current Practice in Neonatal and Paediatric Surgery
Manchester, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

8–9 July 1993
Surgical Research Society Meeting
Dundee, UK
Information. Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

8–10 July 1993
XVIIIth International Update on Liver Disease
London, UK
Information: Professor N. McIntyre, University Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

8–10 July 1993
5th South-east European Symposium of Paediatric Surgery
Graz, Austria
Information: Professor M. E. Höllwarth, Department of Paediatric Surgery, University of Graz, Heinrichstraße 31, A-8010 Graz, Austria

6–8 August 1993
First Asian Pacific Congress of Endoscopic Surgery
Singapore
Information: Maggie Phang, Congress Secretariat, Conference and Exhibition Management Services, 09-43 World Trade Centre, Singapore 0409

22–27 August 1993
International Surgical Week – 35th World Congress of the International Society of Surgery
Hong Kong
Information: Congress Secretariat, ISW Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

27–29 August and
30 August–2 September 1993
Second International Conference of Gastroenterology
Hong Kong and Chengdu, China
Information: Conference Secretariat, Room 1611-13, World Finance Centre, North Tower, Harbour City, Kowloon, Hong Kong

1–3 September 1993
4th International Congress – International Organization for Statistical Studies on Diseases of the Oesophagus
Paris, France
Information: Michele Liegeon, 2 Boulevard de Montparnasse, 75 015 Paris, France

7–10 September 1993
6th International Congress on Interventional Ultrasound
Copenhagen, Denmark
Information: Dr C. Nolsøe, Department of Ultrasound, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

15–18 September 1993
Eurosurgery '93
London, UK
Information: Professor J. P. S. Lumley, Secretariat, Eurosurgery '93, The Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, UK

Instructions to authors

The British Journal of Surgery publishes original articles, reviews and leading articles. Short notes, case reports and surgical workshops are also accepted. All manuscripts are submitted to editorial review.

An article is reviewed for publication on the understanding that the work it reports has not been submitted simultaneously to another journal, has not been accepted for publication elsewhere and has not already been published. **Any detected attempt at dual publication will lead to automatic rejection and may prejudice acceptance of future submissions.** Articles and their illustrations become the property of the Journal unless rights are reserved before publication. The title page should indicate if the paper is based on a previous communication to a society or other meeting. Authors are requested to send three copies of original articles and other editorial matter to: The Senior Editor, *The British Journal of Surgery*, Butterworth-Heinemann Ltd, 59/60 Grosvenor Street, London W1X 9DA, UK. Telephone: 071-493 5841. Facsimile: 071-499 3384.
Books for review should be sent to the same address.

A covering letter must accompany all submissions and must be signed by all authors. The covering letter should state if an abstract of the work has been published and whether the authors wish the manuscript and/or illustrations to be returned if the work is not accepted. The first named author is responsible for ensuring that all authors have seen and approved the manuscript and are fully conversant with its contents.

Rejected manuscripts will not be returned to the authors, unless this is specifically requested.

Ethics

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Preparation of manuscripts

The British Journal of Surgery subscribes to the policy of uniform requirements for manuscripts which is designed to permit authors to resubmit papers to journals without extensive recasting. Authors are advised to consult the *British Medical Journal* 1988; **296**: 401–5 or the *Annals of Internal Medicine* 1988; **108**: 258–65, or to obtain the leaflet 'Uniform Requirements for Manuscripts Submitted to Biomedical Journals' from The Editor, British Medical Journal, BMA House, Tavistock Square, London WC1H 9JR, UK (cost £1·00 per copy).

Authors are responsible for the accuracy of their report including all statistical calculations and drug doses. **When quoting specific materials, equipment and proprietary drugs, authors must state in parentheses the name and address of the manufacturer.** Failure to do so will result in delay in publication as the Journal considers that this information is essential for any reader who wishes to obtain similar material. Generic names should normally be used.

Original articles

Original articles should normally be in the format of introduction, methods, results, discussion. Each manuscript should contain a summary on a separate page. Authors are reminded that there is considerable pressure on editorial space in the Journal. Lengthy manuscripts are likely to be returned to authors for shortening. The discussion in particular should be clear and concise, and should be limited to matters arising directly from the results. Authors should avoid discursive speculation.

Reviews

The Editorial Board of *The British Journal of Surgery* encourages submission of review articles on topics of interest to its readers. Any topic will be considered, but priority will be given to those addressing a major current problem. The author of each accepted review will receive an honorarium. Potential authors seeking advice on the suitability of review topics are advised to contact: Mr J. A. Murie, University Department of Surgery, The Royal Infirmary, Edinburgh EH3 9YW, UK.

Leading articles

The Editors commission signed leading articles to *The British Journal of Surgery*. These articles are 600–1000 words in length, address controversial topics of current interest and are supported by key references. Submissions may be subjected to external review and assessment by the Editorial Board before acceptance. The Editors retain the right to alter style and shorten material for publication. An honorarium is payable on publication.

Short notes

These are original observations presented in brief form. They should follow the standard format of introduction, methods, results and discussion, but no summary is required. Short notes should not exceed 500 words with a maximum of five references and one table or one figure.

Case reports

The British Journal of Surgery receives an increasing number of case reports each year. Space within the Journal remains at a premium and the rejection rate is high. Case reports should be no more than 500 words, with no more than five references and one illustration.

Surgical workshops

These describe technical innovations or modifications which may be useful in surgical practice. These articles should be less than 500 words long; they may be accompanied by no more than two figures and up to five references.

Typescripts

It is *essential* that manuscripts be clearly reproduced with adequate space for editorial notes. **Papers must be typewritten or printed on A4 paper (210 × 297 mm) on one side of the paper only with double spacing and 4 cm margins. Manuscripts which do not conform to these requirements will be returned to the authors for recasting.** Each of the following sections should begin on a new page: title page, summary, text, acknowledgements, references, tables, legends for illustrations. The text should usually follow the standard sequence of introduction,

methods, results and discussion. These sections should run sequentially through the text, avoiding blank space between them.

Title page

The title page should give: (1) the title of the article; (2) the name and initials of each author; (3) the department and institution to which the work should be attributed; (4) the name and address of the author responsible for correspondence and to whom requests for reprints should be addressed; (5) sources of financial support; and (6) the category in which the manuscript is being submitted (original article, case report etc.).

Summary

The second page of the manuscript should carry a summary of not more than 150 words. It should embody the purposes of the study or investigation, basic procedures (study material and observational and analytical methods), main findings (with specific data and their statistical significance, if possible) and the principal conclusions.

Tables and illustrations

Three copies of all illustrations and tables should be submitted. Each table with an appropriate brief title should be typed on a separate page. At least one set of illustrations (line drawings, radiographs, photomicrographs etc.) should be submitted in the form of glossy prints, original transparencies, or negatives and should not be mounted. Photocopies should be of sufficient quality to enable the Journal's referees to judge their content and value. Each illustration should have a label pasted on the reverse side giving its number (to correspond with its reference in the text) and the name(s) of the author(s); the top of the illustration should be indicated. Illustrations should be drawn and labelled appropriately for reduction to one or two column widths of the Journal. Explanations of symbols and shading used should appear in the legend. Survival curves should be accompanied by a table giving the actual numbers of patients involved. The legends to illustrations and the footnotes to tables should contain brief but comprehensive explanations of the information contained therein. Prospective authors are strongly advised to refer to recent issues of the Journal for examples of accepted layout. A contribution towards the cost of colour reproduction is usually requested. If a table or an illustration has been reproduced from a published work the original source thereof must be given in full. Permission to use published work must be obtained from the original author and the publisher before submission.

Abbreviations

Authors should limit the use of abbreviations. Terms which are mentioned frequently may be abbreviated but only if this does not detract from reader comprehension. Abbreviations should be used consistently throughout the text and must be clearly defined on first use.

Numbers and units

The decimal point, not a comma, is used, e.g. 5·7. A space and not a comma follows thousands and multiples thereof, e.g. 10 000. SI units (International System of Units) should be used except for the measurement of blood pressure (mmHg). Where measurements were made in non-SI units, the actual values and units should be given, with SI equivalents inserted in parentheses at appropriate points.

References

References should be typed with double spacing and cited in the Vancouver style (see above: Uniform Requirements for Manuscripts Submitted to Biomedical Journals). Reference to abstracts from meetings is discouraged; reference to unpublished communications is not acceptable. Personal communications should be cited in the text, in parentheses. The first author is responsible for confirming the acceptability of the material quoted with the originator.

In the text, references should be numbered consecutively by superscript: ^{1,2} or $^{1-3}$. References cited only in tables or figures should be numbered in sequence according to the first mention of the table or figure in the text. The sequence for a standard journal article should be: author(s); title of paper; journal name abbreviated as in Index Medicus (written in full if no abbreviation quoted) and year of publication; volume number; page numbers. For example: De Bolla AR, Obeid ML. Mortality in acute pancreatitis. *Ann R Coll Surg Engl* 1984; **66**: 184–6. The sequence for the chapters of a book should be: author(s); chapter title; editors; book title; place of publication; publisher; year of publication; page numbers. For example: Calenoff L, Rogers L. Esophageal complications of surgery and lifesaving procedures. In: Meyers M, Ghahremani G, eds. *Iatrogenic Gastrointestinal Complications.* New York: Springer-Verlag, 1981: 123–63.

Statistics

For detailed guidance on the handling of statistical material, authors should consult *The British Journal of Surgery* 1991; **78**: 782–4. The Editors and statistical referees in evaluating a manuscript will consider the *design* of the study, the *presentation* of the data, the *analysis* of the data, and the *interpretation* of the results.

Design

Authors should set out clearly the objectives of the study, should identify the primary and secondary hypotheses, and should explain the rationale for the choice of sample size.

Presentation

Whenever possible a graphical presentation should be used to illustrate the main findings of a study. The use of standard deviation and standard error should be clearly distinguished. The use of the '±' symbol should be avoided; these statistics should be presented in parentheses after the mean value.

Analysis

There should be a clear description of which methods were used for which analyses, and any methods not in common usage should be supported by references. Results of statistical tests should be reported by stating the value of the test statistic, the number of degrees of freedom and the P value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Actual P values should be reported, to two decimal places, especially when the result is not significant, rather than stating 'not significant'.

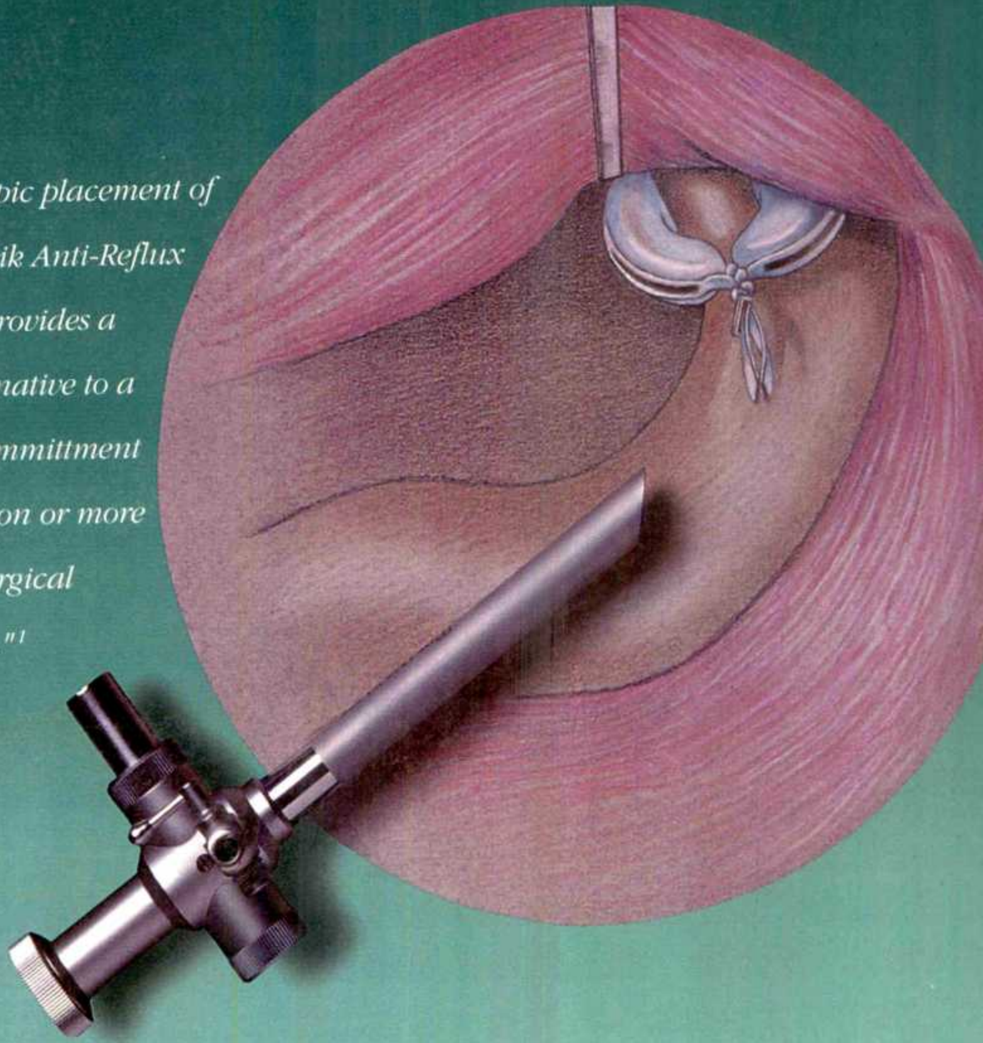
Whenever possible, the results of the primary analyses should be reported using confidence intervals instead of, or in addition to, P values.

Interpretation

Statistical significance should not be confused with clinical significance. In particular, 'negative' findings should be interpreted through the use of confidence intervals.

Authors should beware of placing undue emphasis on secondary analyses, especially when they were suggested by an inspection of the data.

Laparoscopic Treatment of Gastroesophageal Reflux



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[1] MacPhee, W.,"Laparoscopic Placement of the Angelchik Anti-Reflux Prosthesis." Submitted for presentation, 3rd World Congress of Endoscopic Surgery, Bordeaux, France. 1992.

[2] Angelchik, J.P.et al., "The Anti-Reflux Prosthesis: Simple, Effective Therapy for Gastroesophageal Reflux." Chapter 5 in **Debates in Clinical Surgery**, Volume 2, Simmons RL and AO Udekwa, eds., Mosby Year Book, St. Louis, 1991.

[3] Timoney, A.G. et.al., "The Angelchik Anti-Reflux Device: a 5-Year Experience" **Annals of Royal College of Surgeons of England**, 72: 185-187, 1990.

[4] Petterson,G.B., et.al., "The Dynamics of Lower Esophageal Sphincter Function" **Current Surgery**, 37: 143-145, 1980.

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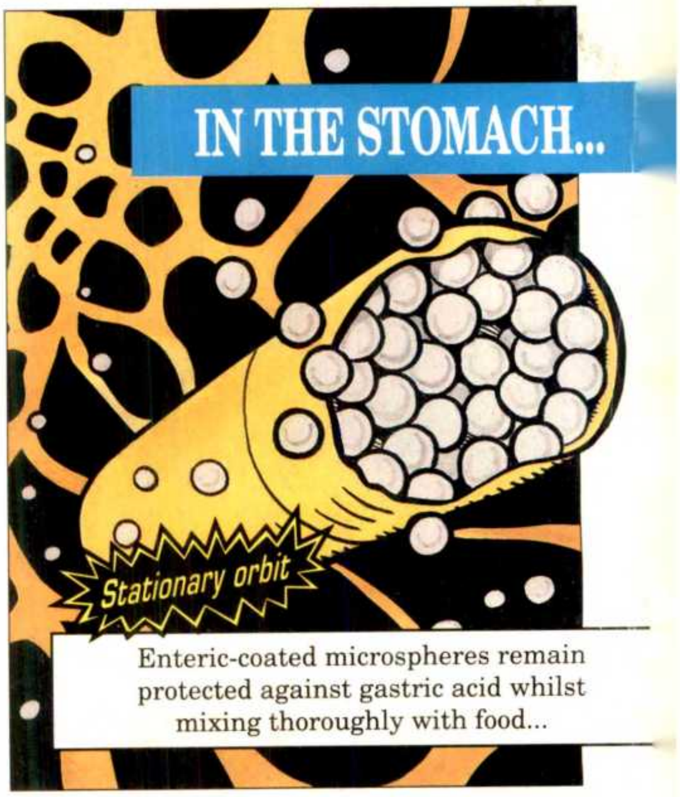

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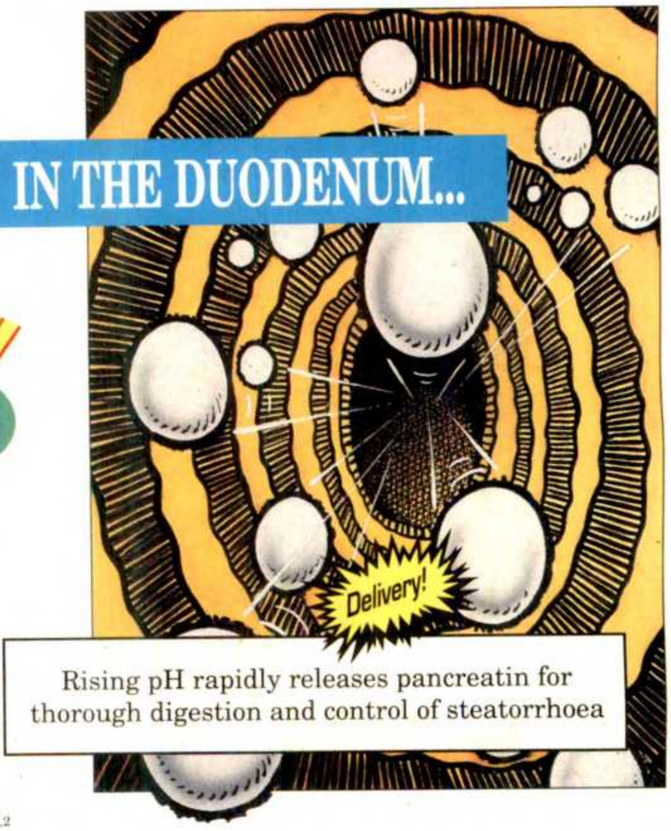
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References
1. Stead R J et al. *Thorax* 1987; **42**: 533-37
2. Beverley D W et al. *Arch Dis Child* 1987; **62**: 564-68

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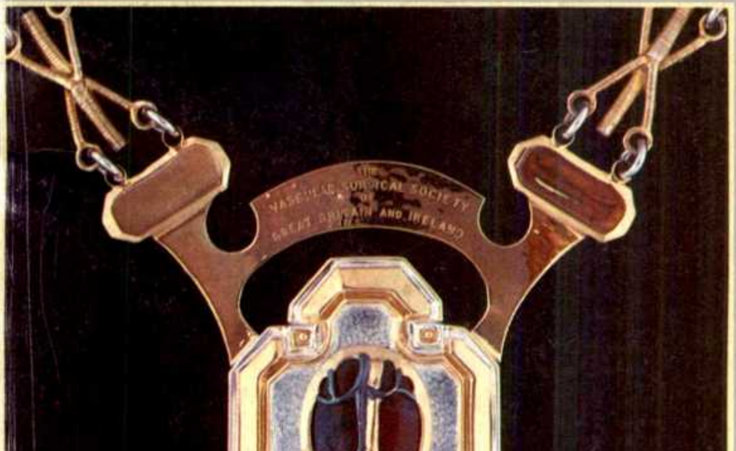
Volume 80 Number 4 April 1993



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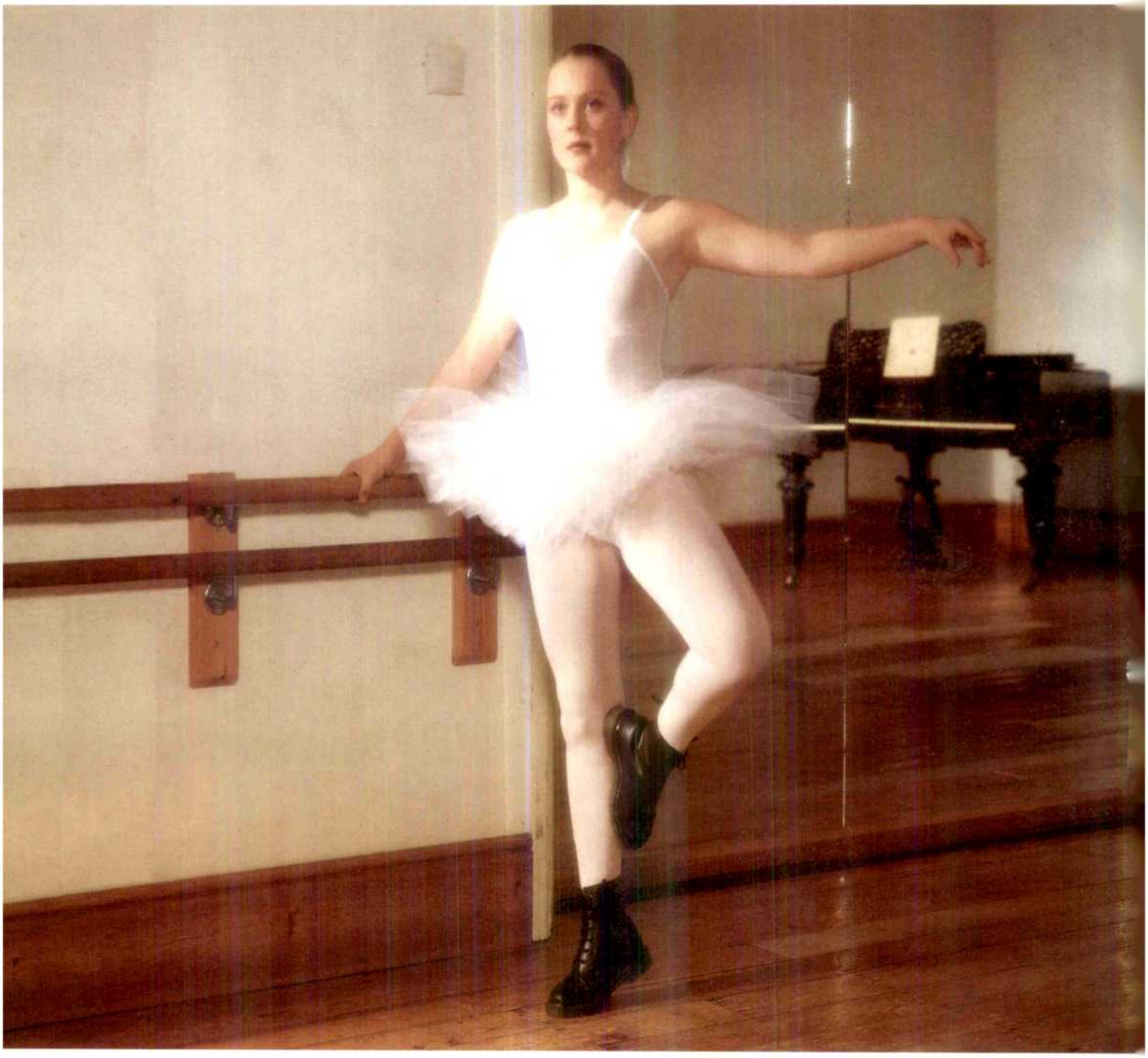

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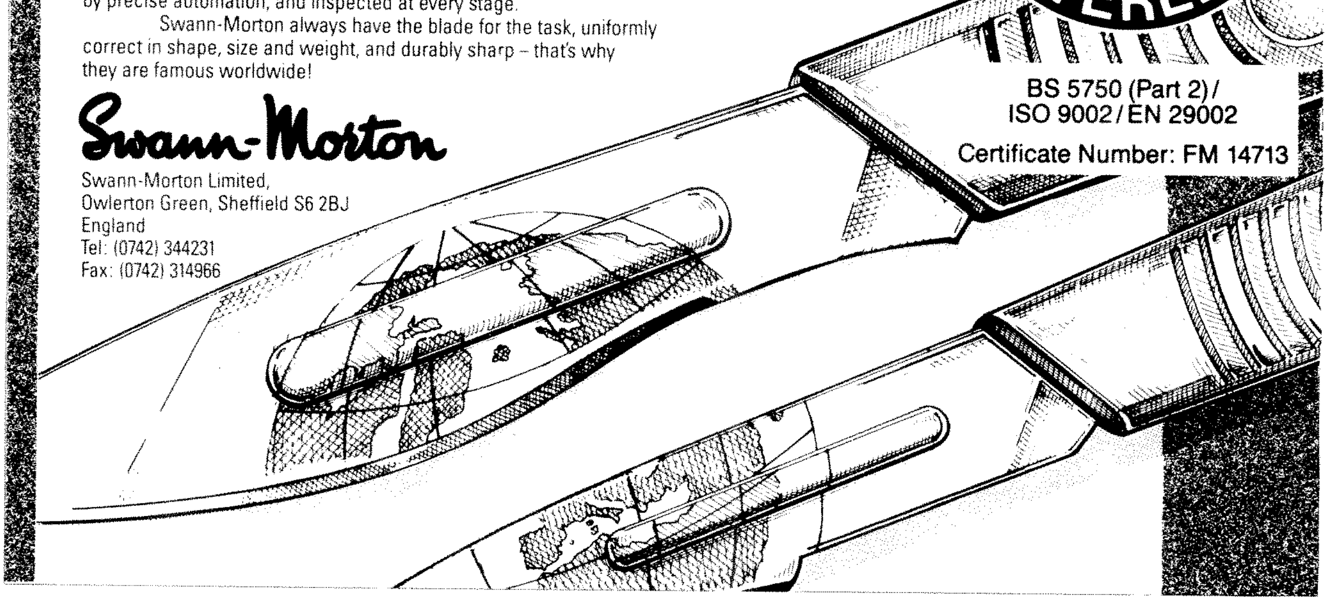

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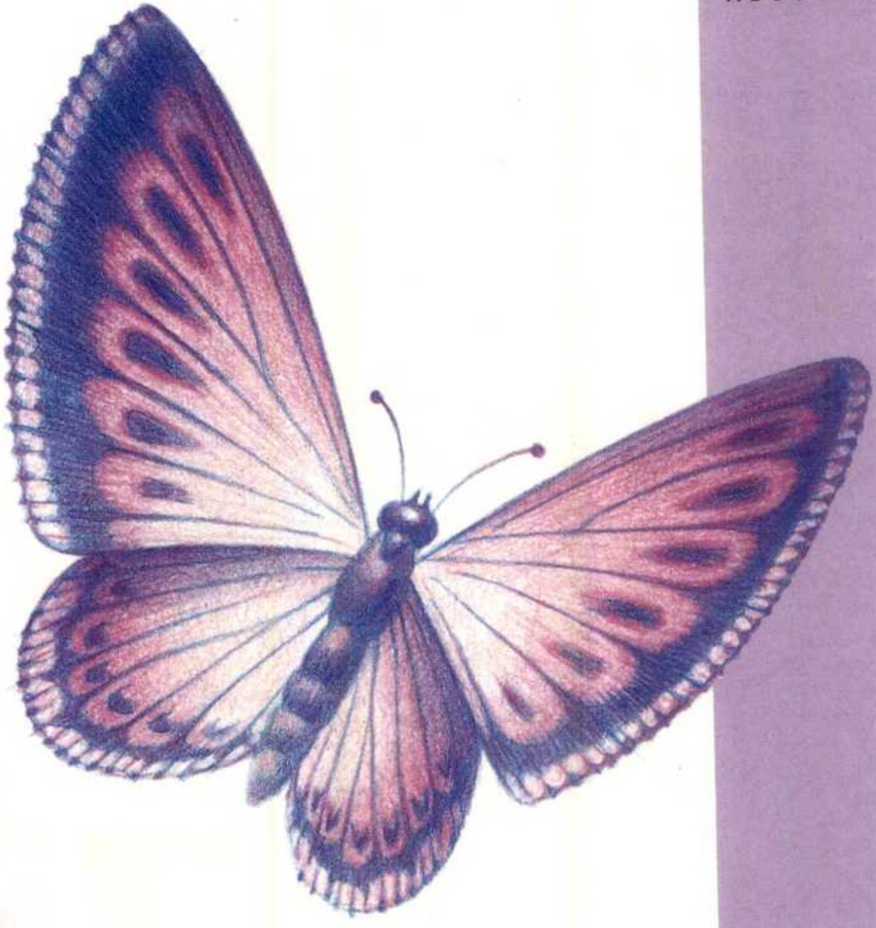

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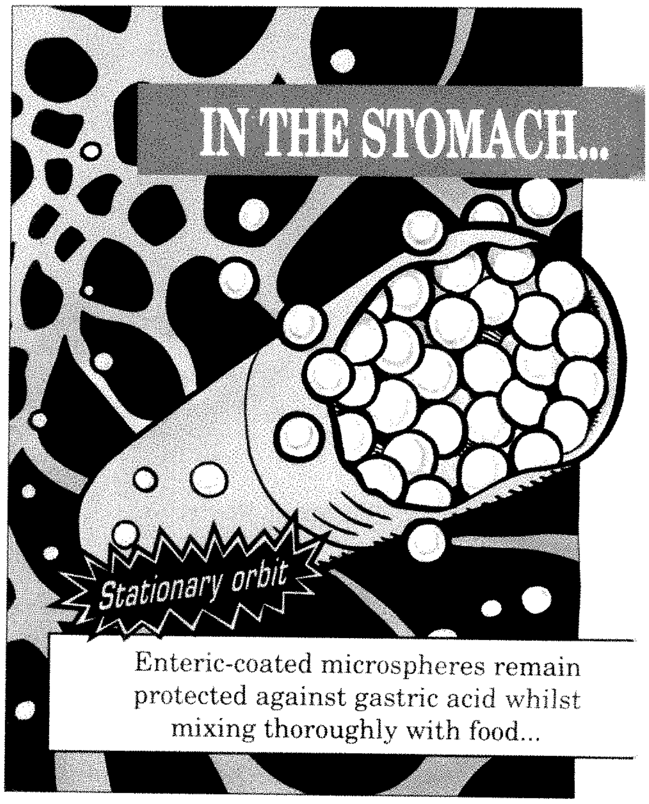
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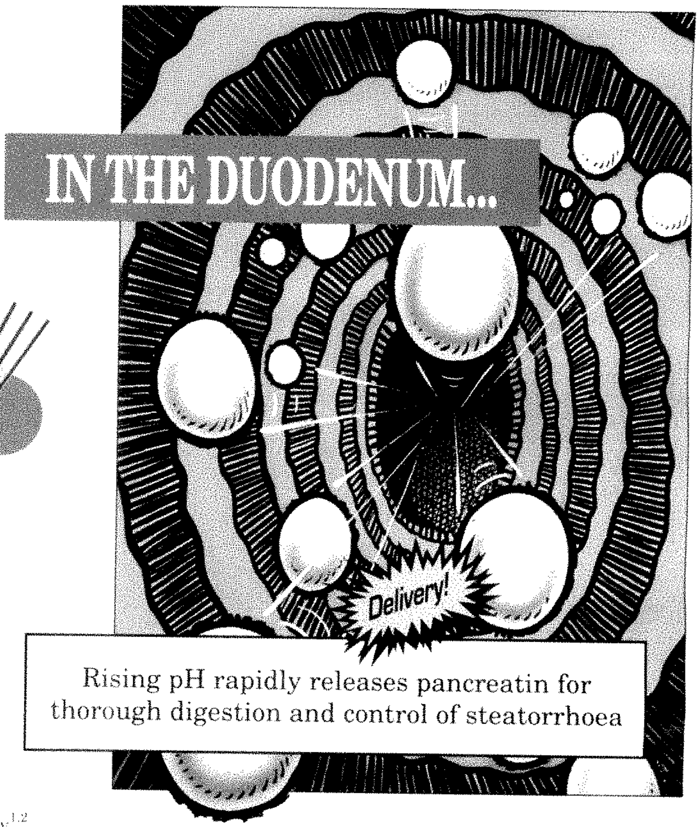
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The last of the Journal's Board Members from Great Britain and Ireland.

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Lymphatic fistula and perigraft seroma

Lymphatic fistula and perigraft seroma after vascular surgery are uncommon complications about which little has been written; surgeons' knowledge of these conditions is limited and management anecdotal. This article incorporates the philosophy of an individual vascular unit in the light of experience and the currently available literature.

Lymphatic fistula

A lymphatic fistula is a persistent watery discharge that complicates approximately 2 per cent of vascular surgical incisions in the groin[1]. The highest incidence of lymphatic fistula is in the critically ischaemic limb in which increased interstitial fluid, caused by limb dependency and leakage from damaged capillaries, results in an increased lymph flow through disrupted groin lymphatics[2]. Secondary groin exploration is also associated with the development of lymphatic fistula, and femoropopliteal surgery carries a higher risk than proximal reconstructive procedures[2], probably because of disruption of superficial lymphatics related to the long saphenous vein. The volume of lymph leak is variable, occasionally exceeding 500 ml in 24 h; without surgical intervention the leak usually resolves within 28 days and spontaneous resolution is the norm[1,2]. The discharged lymph is initially sterile but in approximately 25 per cent of patients cultures become positive[2]; *Staphylococcus epidermidis* is more commonly isolated than more pathogenic organisms such as *Pseudomonas aeruginosa*. Clinical evidence of wound infection is less frequent than may be expected from the incidence of positive lymph cultures and in a series of 35 patients with lymph leaks Murphy *et al.*[2] found no evidence of graft infection. In contrast, Kwann *et al.*[1] described graft infection leading to amputation in the presence of an infected lymphatic fistula. Since lymphatic leaks are commonly associated with some degree of wound dehiscence, all lymphatic fistulas should be regarded as potential causes of graft infection.

Certain measures may reduce the incidence of lymphatic fistula. Administration of subcutaneous heparin in the scapular region, away from the drainage field of the groin lymphatics, may prevent the increase in inguinal lymph flow associated with the local administration of this agent. The lateral approach to the common femoral artery avoids the deep inguinal nodes and minimizes division of lymphatic channels in the groin. Closure of a groin incision should include at least one, and preferably two, layers of subcutaneous tissue so as to strangulate the lymphatics.

A low-output fistula should be managed conservatively by bed-rest and tamponade. Bed-rest reduces lymph flow through the leg, facilitating nursing care of the groin incision and providing a rational basis for lymphostasis. A persistent high-output fistula requiring daily dressing changes should be managed surgically. Patent blue dye, injected as multiple subcutaneous blebs across the mid-thigh, aids identification of the site of a leak in the groin, and damaged lymphatics are either ligated or under-run using an absorbable suture. Suction drains should be avoided as they may encourage persistence of the lymphatic fistula. In addition to its antibacterial action, tetracycline is acidic and its local administration may encourage an inflammatory reaction leading to fibrosis and cicatrization of damaged lymphatics.

Perigraft seroma

A perigraft seroma is a collection of clear, sterile fluid surrounding a bypass graft. This complication is uncommon: few individual surgeons have reported more than four cases[3]. The great majority of perigraft seromas occur around Dacron (Du Pont, Stevenage, UK) and polytetrafluoroethylene grafts, although a small number of non-porous grafts have been affected. Subcutaneous bypass grafts seem particularly prone to this problem and over 50 per cent of reported cases are related to axillofemoral reconstruction. The apparent low incidence of perigraft seroma around deeper-sited reconstructions may, however, arise simply from difficulty in detection[4].

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The seroma is most commonly localized around the middle and distal portions of the graft, although the entire graft may be involved[3].

Biochemical similarities with serum have encouraged most workers to regard seroma fluid as an ultrafiltrate of blood[5]. The containing pseudocapsule is a fibrous structure, with a thin inner secretory membrane loosely adherent to the outer surface of the graft, which contains immature fibroblasts[6]. The presence of other cellular components, notably inflammatory cells, is controversial[7]. The overall impression of a poorly incorporated graft bathed in an ultrafiltrate of blood has encouraged rival aetiological theories. Faulty graft incorporation may be due to a humoral fibroblast inhibitor that prevents maturation and proliferation of perigraft fibroblasts[6,8], or a specific immunological reaction may be mounted against the graft[7]. Alternatively, abnormal graft porosity may be caused by a number of factors, including trauma, soilage by lipophilic molecules or possibly by variation in quality control at the time of graft manufacture[3].

A perigraft seroma should be regarded as a late complication of surgery, since fluid collections are common until synthetic grafts become encapsulated at about 6 weeks after operation. Spontaneous resolution occurs in approximately 65 per cent of selected cases[3]. A perigraft seroma is commonly painless, but stretching of the overlying skin can cause discomfort and erythema which may indicate impending ischaemic ulceration. This must be distinguished from abscess, haematoma or pseudoaneurysm. There is no evidence that perigraft seroma is primarily infected[7]; septic complications are probably due to repeated aspiration or surgical intervention. Similarly, graft thrombosis has been described only in series in which the surgeon has intervened. There is no evidence to suggest graft compression by perigraft seroma.

In a comprehensive survey[3], 22 cases (9 per cent) of perigraft seroma were managed by 'observation only' and infection or thrombosis complicated only one case. Based on this limited information on natural history, the principal approach to a perigraft seroma should be one of observation only. The efficacy of plasmaphaeresis, designed to eliminate a humoral fibroblast inhibitor[8], remains unconfirmed in extensive clinical experience. Aspiration is associated with an unacceptably high incidence of infection and should be reserved for situations in which there is diagnostic doubt. Surgery is indicated only for pain or marked erythema of the overlying skin. There have been isolated reports of evacuation of the seroma and packing of the cavity with microfibrillar collagen[9,10]. Some surgeons have suggested removal of the existing graft and reconstruction using a different prosthetic material, through a new anatomical route. Such treatment is associated with a recurrence rate of < 10 per cent and a low incidence of infection[3], but the need for such a radical approach must be questioned. Local excision of the seroma, including the fibrous capsule, may lead to skin necrosis, graft infection, recurrence of the seroma and graft thrombosis[3]. Seroma excision is, therefore, generally unwise.

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1. Kwann JHM, Bernstein JM, Connolly JE. Management of lymph fistula in the groin after arterial reconstruction. *Arch Surg* 1979; **114**: 1416–18.
2. Murphy JL, Cole CN, White PM *et al.* Lymphatic fistula after vascular reconstruction: a case–control study. *Can J Surg* 1991; **34**: 76–8.
3. Blumenberg RM, Gelfand ML, Dale WA. Perigraft seromas complicating arterial grafts. *Surgery* 1985; **97**: 194–203.
4. Qvarfordt PG, Reilly LM, Mark AS *et al.* Computerized tomographic assessment of graft incorporation after aortic reconstruction. *Am J Surg* 1985; **150**: 227–31.
5. Borrero E, Doscher W. Chronic perigraft seromas in PTFE grafts. *J Cardiovasc Surg (Torino)* 1988; **29**: 46–9.
6. Ahn SS, Machleder HI, Gupta R *et al.* Perigraft seroma: clinical, histological and serologic correlates. *Am J Surg* 1987; **154**: 173–8.
7. Kaupp HA, Matulewiecz IJ, Lattimer GL *et al.* Graft infection or graft reaction? *Arch Surg* 1979; **114**: 1419–22.
8. Sladen JG, Mandl MAJ, Grossman L *et al.* Fibroblast inhibition: a new and treatable cause of prosthetic graft failure. *Am J Surg* 1985; **149**: 587–90.
9. Rhodes VJ. Perigraft seroma: simple solution to a difficult problem. *J Vasc Surg* 1986; **3**: 939 (Letter).
10. Blumenberg RM. Invited commentary in lymph fistulas and seromas. In: Dale WA, ed. *Management of Vascular Surgical Problems*. Maidenhead: McGraw-Hill, 1985: 293–8.

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Non-surgical treatment of cancer of the oesophagus

The majority of patients with oesophageal cancer are unsuitable for surgical treatment because of tumour spread, associated medical problems or age. The predominant symptom is difficulty in swallowing of a degree that varies but eventually progresses to complete dysphagia. Without some form of palliation these patients have a poor quality of life, rapid weight loss and an unpleasant death. The aim of palliation is the complete relief of dysphagia with minimum morbidity and maximum quality of life both during and after treatment. Although quality, rather than quantity, of life is more important, for many patients survival will be prolonged because of improved nutrition as a result of treatment.

Palliative treatments may be broadly divided into endoscopic techniques that relieve obstruction of the oesophageal lumen, and radiotherapy and chemotherapy that may, in addition, alter the natural history of the disease. An increasing number of palliative methods have been described in recent years; it is now appropriate that the use of palliation is examined critically so that the best method or combination of methods may be properly recommended for an individual patient.

Oesophageal dilatation alone is an inadequate treatment as dysphagia returns rapidly. Oesophageal intubation remains the most commonly used method[1] as this may be accomplished at one treatment session and provides immediate relief of dysphagia. Intubation should always be performed endoscopically and under fluoroscopic control. In cases complicated by tracheo-oesophageal fistula or external compression, intubation is the treatment of choice. Although with good aftercare a soft nutritious diet is possible, swallowing after intubation never returns to normal. Tubes may become displaced or blocked by food or tumour overgrowth, but these problems can usually be solved by further endoscopic manoeuvres. Endoprostheses have limitations: if placed across the cardio-oesophageal junction they produce incapacitating reflux and they cannot be placed close to the cricopharyngeal sphincter for upper-third tumours.

The other major palliative endoscopic technique is tumour necrosis, using laser, diathermy or the injection of a cytotoxic substance. Laser recanalization involves vaporizing tumour using the neodymium yttrium–aluminium–garnet laser. Exophytic tumours are more suitable for laser therapy. A delay of up to 1 week between initial treatment and relief of dysphagia is typical and regrowth of tumour always requires visits for further treatment. In a prospective non-randomized comparison of laser recanalization *versus* intubation[2], the palliation of dysphagia was similar for both but the oesophageal perforation rate was significantly lower after laser treatment (2 *versus* 13 per cent); laser-treated patients underwent more procedures and had longer overall hospital stays. Bipolar diathermy has also been used to destroy circumferential oesophageal tumours and is cheaper than laser therapy; it has been shown to be as efficacious and safe as laser treatment[3]. Tumour necrosis following endoscopic injection of absolute ethanol is the most recently described technique for oesophageal recanalization but, to date, there have been few publications on its use[4].

In contrast to endoscopic methods, radiotherapy offers a chance to inhibit the local progression of the primary cancer. While radiation may be given by external beam or by an intraluminal source, it has traditionally been administered by the former method. The optimum dose for this route is unknown, but the minimum accepted for radical treatment is 5000 cGy as more than 6000 cGy causes unacceptable side-effects. With a daily dose of 200 cGy and five treatments per week, a full course of treatment lasts 5 weeks, but up to 20 per cent of patients are unable to complete this because of poor tolerance. The relief of dysphagia may take several weeks. The generalized debilitating effects of radiotherapy may detract from the quality of life remaining to the patient, and stricture and oesophagorespiratory fistula may occur after irradiation. Pearson's 1-year survival rate of 44 per cent and 5-year survival rate of 22 per cent with radiotherapy as the primary treatment of squamous cancer have never been reproduced[5]. Adenocarcinoma of the oesophagus has often been considered to be radioresistant but there are data showing little difference in survival rates between patients with adenocarcinoma and those with squamous carcinoma affecting the cardia treated with radiotherapy[6]. This is particularly relevant because adenocarcinoma of the cardia is increasing in incidence.

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Intracavity irradiation (brachytherapy) is arousing interest as a result of the development of the Selectron (Nucleotron, Zeersum, Holland) remote-control afterloading machine, which makes the procedure simple and safe[7]. The Selectron applicator tube is passed over an endoscopically placed guidewire and positioned across the tumour using fluoroscopy. The applicator is fixed at the mouth and the patient is transferred to a protected treatment room and connected to the Selectron machine. A microprocessor controls the pneumatic transfer of caesium-137 pellets down a flexible tube inserted into the applicator. Treatment is given as a single fraction of 1500 cGy for rapid palliation. The great merit of brachytherapy is that the radiation dose is highest to the tumour while adjacent normal tissues are relatively spared. The combination of a lower dose of external-beam radiotherapy with brachytherapy is an attractive new development, but so far there are few published data on such therapy and no randomized trials. Although chemotherapy alone has no apparent place in oesophageal cancer treatment, reports of a combined regimen of chemotherapy and radiotherapy have been more encouraging[8]. Intraluminal debulking in combination with external-beam radiotherapy may allow prolonged palliation and perhaps longer survival. Although such treatment combinations may confer benefit, they must be subjected to the scrutiny of the controlled trial, with objective data being collected on both quality of life and palliation of dysphagia.

Recurrent problems with swallowing after both surgical and palliative treatment are common. These are not always due simply to mechanical obstruction; they may also arise from recurrent laryngeal nerve palsy resulting in aspiration on swallowing[9]. When intraluminal recurrence occurs after oesophagectomy, laser recanalization of the exophytic growth is the treatment of choice.

Clearly, there are a number of different therapeutic options for the treatment of the obstructed oesophageal lumen. There are also new methods of potentially altering the natural history of the disease. Now is the time to determine which treatment or treatment combination is best for individual patients. In the future, quality of life and survival benefits can be established only if the assessment of palliation is better documented. All future trials must use a clearly defined dysphagia grading system alongside an objective assessment of quality of life during the follow-up period of all patients with treated tumours. Randomized controlled trials of combinations of treatments, particularly including intraluminal radiotherapy, are long overdue, and the role of brachytherapy must be established. The first clinical trial should compare endoscopic intubation alone (the most commonly performed palliative manoeuvre) with a combination of intubation, brachytherapy and low-dose external-beam radiotherapy. It may even be shown eventually that palliative treatment can provide a better result, in terms of quality and quantity of life, than attempted curative surgical resection.

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1. Ogilvie AL, Dronfield MW, Ferguson R, Atkinson M. Palliative intubation of oesophagogastric neoplasms at fibreoptic endoscopy. *Gut* 1982; **23**: 1060–7.
2. Loizou LA, Grigg D, Atkinson M, Robertson C, Bown SG. A prospective comparison of laser therapy and intubation in endoscopic palliation for malignant dysphagia. *Gastroenterology* 1991; **100**: 1303–10.
3. Jensen DM, Machicado G, Randall G, Tung LA, English Zych S. Comparison of low power YAG laser and bicap tumour probe for palliation of oesophageal cancer strictures. *Gastroenterology* 1988; **94**: 1263–70.
4. Payne-James JJ, Spiller RC, Misiewicz JJ, Silk DBA. Use of ethanol induced tumour necrosis to palliate dysphagia in patients with oesophagastric cancer. *Gastrointest Endosc* 1990; **36**: 43–6.
5. Pearson JG. The radiotherapy of carcinoma of the oesophagus and post-cricoid region in South East Scotland. *Clin Radiol* 1966; **17**: 242–57.
6. Agrawal RK, Dawes PJDK, Clague MB. Combined external beam and intracavitary radiotherapy in oesophageal carcinoma. *Clin Oncol* (*R Coll Radiol*) 1992; **4**: 222–7.
7. Rowland CG, Pagliero KM. Intracavitary irradiation in palliation of carcinoma of oesophagus and cardia. *Lancet* 1985; **ii**: 981–3.
8. Gill PG, Jamieson GG, Denham J *et al.* Treatment of adenocarcinoma of the cardia with synchronous chemotherapy and radiotherapy. *Br J Surg* 1990; **77**: 1020–3.
9. Griffin SM, Chung SCS, Van Hassalt CA, Li AKC. Late swallowing and aspiration problems after esophagectomy for cancer. Malignant infiltration of the recurrent laryngeal nerves and its management. *Surgery* 1992; **112**: 533–6.

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Diagnostic value of cytology for biliary stricture

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Over the past 20 years, bile aspiration at endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography has been developed for cytological diagnosis of biliary tract stricture. This safe and specific test has allowed a diagnosis to be reached before or without operation in about one-third of malignancies of the pancreas or biliary tree. The recent development of biliary brush cytology has produced better results. An endobiliary biopsy forceps is now available that may allow safe sampling of lesions causing extrinsic compression of the biliary tract. An endobiliary aspiration cytology needle has been produced that may permit non-ulcerating lesions to be diagnosed. A safe alternative to endobiliary methods is percutaneous fine-needle aspiration cytology; this yields a diagnosis in about half of patients presenting with obstructive jaundice and an imaged mass lesion.

There are many causes of bile duct stricture (*Table 1*) and differentiating benign from malignant may be difficult, even in a specialized centre. History, physical examination and biochemical tests are usually unhelpful. Ultrasonography and computed tomography (CT) may establish the presence of biliary obstruction in >90 per cent of patients and are reasonably good at predicting the level of the obstruction (ultrasonography, 60 per cent; CT, 90 per cent)[1]. However, these imaging methods correctly predict the underlying pathology in only one-third (ultrasonography) to two-thirds (CT) of patients[1]. As would be expected, the results are best for biliary obstruction caused by a pancreatic mass and worst for cholangiocarcinoma without a mass lesion. Although combining imaging methods may increase diagnostic accuracy, it remains below that required for making satisfactory clinical decisions and the preoperative imaging diagnosis is often incorrect[2,3]. Endoscopic retrograde cholangiopancreatography (ERCP) and percutaneous transhepatic cholangiography (PTC) allow the site of a lesion within the biliary tree to be established but give little information about its nature[2]. Angiography may show evidence of tumour circulation or vascular invasion but it is invasive, expensive, time consuming, potentially dangerous and probably inappropriate unless a patient is being considered for surgery. New imaging methods such as nuclear magnetic resonance and positron emission tomography have yet to establish their role.

Obtaining tissue for diagnosis is difficult in the biliary tree but is essential to allow decisions to be taken on treatment and to assess prognosis; when obtained early it may obviate the need for subsequent investigation. Newer forms of treatment, such as liver transplantation for sclerosing cholangitis or balloon-dilatation for benign biliary stricture, demand accurate pretreatment diagnosis to prevent their inappropriate use for malignant disease[4]. A 'no tissue' diagnosis is no longer acceptable in the management of patients with biliary stricture. Histological examination, although theoretically ideal since it should give information on both tumour depth and grade, is impractical in most cases. In the few patients with bile duct stricture for whom histological information is obtained before operation, biopsy usually provides little information other than whether there is or is not neoplasia. This has encouraged the use of cytology.

This review analyses the contribution of cytology to the diagnosis of biliary tract stricture. It covers criteria for cytological diagnosis, results of cytology from duodenal aspirate, sampling at ERCP and PTC, percutaneous and intraoperative fine-needle aspiration cytology (FNAC) and recent innovations in endobiliary brushing, biopsy and FNAC. All appropriate literature written in English and documented in or referred to in *MEDLINE* was reviewed. The data presented therein were analysed in a standard format to provide a combined total number of patients, number with cancer and number with positive cytology results. For each study the following were calculated[5]: sensitivity (percentage of cytology specimens considered positive in patients with proven malignant disease); specificity (percentage of cytology specimens considered negative in patients free of malignant disease); positive predictive value (percentage of times a positive cytology result will detect a patient with malignancy); negative predictive value (percentage of times a negative cytology result will detect a patient without malignancy); and overall accuracy (percentage of correct positive and negative cytology findings in all patients under investigation). Data from individual studies have also been pooled for each method of obtaining a cytological diagnosis to allow a meta-analysis. This yielded an overall sensitivity, specificity, positive predictive value, negative predictive value and accuracy for each method. Results for the various techniques have been compared between patient groups using the χ^2 test. Because meta-analysis may overlook

Table 1 *Conditions causing biliary tract stricture*

Benign	Malignant
Congenital	Carcinoma of pancreas
Bile duct injury	Cholangiocarcinoma
Postoperative	Ampullary cancer
Blunt or penetrating injury	Liver metastases
Radiotherapy	Hepatocellular cancer
Inflammatory	Gallbladder cancer
Gallstones	Neoplastic hilar lymphadenopathy
Chronic pancreatitis	
Parasitic infection	
Recurrent pyogenic cholangitis	
Liver abscess	
Primary sclerosing cholangitis	
Papillary stenosis	
Benign neoplasm	

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important differences between individual studies, results of each report have also been tabulated; significant variations between results are discussed[6].

Historical background

Since the 1950s cytology has become an established method of obtaining a tissue diagnosis in many clinical areas, including disease of breast, thyroid, cervix, lung and urinary tract[7]. Even in the diagnosis of biliary tract stricture it has been employed for over 40 years, but without becoming widely adopted. This is due mainly to the technical difficulty of obtaining adequate samples and to problems with cell preservation for microscopic assessment. Koss[8] described cytology as 'art and science' because, although scientifically based, much depends on the experience of the individual cytologist.

Biliary tract cytology may be performed on cells freely exfoliated in the bile (bile cytology) or the process may be enhanced by instrumentation, for instance brush cytology. These should be considered separately from non-exfoliative cytology methods, such as FNAC, which has been defined by Bamforth[9] as 'the examination of cells obtained from needle or drill biopsy in solid organs or tissue masses or from the cut surface of such material freshly removed by surgical biopsy'.

Criteria for cytological diagnosis

Normal bile

Before cytology can be used to diagnose biliary neoplasia a precise understanding of normal biliary epithelium is essential. Normal bile contains a few epithelial cells that are well preserved. These occur singly, or in monolayer or folded sheets, and have a columnar or cuboidal configuration. The average diameter of an epithelial cell is 30 μm and cells are fairly uniform in size. Their cytoplasm is lightly opaque, sometimes vacuolated, acidophilic or cyanophilic. The granular nuclei contain a single small nucleolus, which is oval and situated paracentrally towards the basal portion of the cell. Goblet cells can also be seen. Exfoliated cells from the bile and pancreatic ducts are similar.

Effects of inflammation

Inflammation in the biliary tree, resulting from obstruction, infection, foreign body (e.g. calculus or stent) or recent instrumentation, increases the number of epithelial cells in the bile. These cells may undergo non-malignant morphological changes, such as hyperplasia or regenerative or degenerative alteration, making differentiation between benign and malignant lesions difficult. Misdiagnosis after recent instrumentation has been reported[10]. The cytological signs of cell alteration due to inflammation include loss of surface structures, vacuolization of cytoplasm, nuclear enlargement, coarse hyperchromasia, multinucleation and multinucleolation. Cell death is indicated by fragmentation, nuclear destruction (pyknosis, karyolysis, karyorrhexis) and cytoplasmic vacuolization[8]. In acute inflammation bile contains leucocytes, blood, yeasts and bacteria, in addition to normal and abnormal epithelial cells.

Effects of neoplasia

Neoplasia can be established only by careful evaluation of individual cells, their relation to one another, and the general appearance of the smear. Unfortunately, no single feature is diagnostic. Tumour cells usually have an increased diameter and occur in clusters, vary in size (anisocytosis) and exhibit cell engulfment (phagocytosis). The nuclear features are most important. Neoplastic cells show nuclear enlargement or shrinkage in relation to their cytoplasm, causing a change in the nuclear:cytoplasmic diameter ratio. In normal cells this ratio is more or less constant[8] at about 1:3. Irregular clumping of nuclear chromatin and hyperchromasia resulting from increased staining intensity is a significant feature. Other findings include irregular shape and contour of the nucleus, alteration in size, shape and number of nucleoli, occurrence of multinucleate forms and an increase in mitotic figures. Not all changes have to be observed together to diagnose neoplasia but cell and nuclear enlargement, variation in shape and clumping of chromatin are essential characteristics. These strict criteria for the cytological diagnosis of neoplasia are necessary as many cell changes, such as variation in staining reaction, size, shape and vacuolization, may be seen in inflammation. The cytological appearances of neoplastic cells from pancreatic and bile duct carcinoma are similar, making it impossible to determine the organ of origin of such bile-derived cells. Specimens collected by percutaneous FNA are less likely to show cell necrosis than those obtained from the biliary tree. However, cell changes are similar in pancreatic cancer and chronic pancreatitis, so FNAC, in common with histological examination, may produce a false-positive diagnosis of malignancy[11].

Cytology from duodenal aspirates

Since 1920, cytology has been performed on epithelial cells exfoliated into the biliary tract and aspirated from the duodenum. Results from the first large series of patients were published by Lemon and Byrnes[12] in 1949. Duodenal aspiration cytology was carried out in 58 patients with suspected cancer of the biliary tract or pancreas, most of whom presented with jaundice. The method had a sensitivity of 72 per cent with no false-positive result. However, subsequent reports[12,13] on a larger series of patients studied by the same group gave a sensitivity of only 33 per cent. The initial experience of Lemon and Byrnes, and results from eight other major series reported over the next 30 years, are shown in *Table 2*. All reports

Table 2 *Duodenal aspiration cytology in patients with suspected pancreatic or bile duct cancer*

Reference	Year	No. of patients	Patients with cancer	True positive	False positive	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall accuracy (%)
Lemon and Byrnes[12]	1949	58	18	13	0	72	100	100	88	91
Raskin *et al.*[13]	1958	203	43	28	0	65	100	100	91	93
Raskin *et al.*[14]	1959	356	55	33	2	60	99	94	93	93
Bowden and Papanicolaou[15]	1960	132	50	23	0	46	100	100	75	79
Dreiling *et al.*[16]	1960	212	72	59	12	82	92	83	80	89
Nieburgs *et al.*[17]	1962	301	105	43	4	41	98	91	76	78
Goldstein *et al.*[18]	1968	67	24	18	0	75	100	100	88	91
Prolla and Kirsner[19]	1972	2142	187	112	5	60	100	96	96	96
Kline *et al.*[20]	1978	239	40	18	0	45	100	100	90	96
Total		3710	594	347	23	58	99	94	93	93

involved exfoliative cytology performed on samples collected from the duodenum after placement of a nasoduodenal tube. Of 3710 patients sampled, 594 were found to have cancer. The reported sensitivity of cytology varied from 41 to 82 (mean 58) per cent. Successful diagnosis of more than half of patients with pancreatobiliary cancer suggests that duodenal drainage cytology is a useful diagnostic test, but there are problems with these studies. Placement of the duodenal tube is frequently difficult[15] and may take 2–4 h. Detection of neoplastic cells in the duodenal aspirate gives no indication of the site of the neoplasm[20]. Many of the patients studied had advanced disease, such as pancreatic cancer with duodenal ulceration. The results of duodenal aspiration cytology in current practice would undoubtedly be poorer. The major difficulty, however, with cytological diagnosis from duodenal aspirates is that duodenal juice mixed with exfoliated cells produces degenerative alterations that can be mistaken for malignant change. This may explain why many series have included a few patients with false-positive results (*Table 2*) and in some studies 5–10 per cent of control patients had positive findings on cytology. The potential for obtaining false-positive results, and the introduction of more direct methods for obtaining bile or pancreatic juice, have made duodenal aspiration cytology of only historical interest.

Cytology sampling at endoscopic retrograde cholangiopancreatography and percutaneous transhepatic cholangiography

The introduction of the diagnostic and therapeutic biliary tract procedures of ERCP and PTC in the early 1960s allowed the collection of bile or pancreatic juice straight from the bile or pancreatic duct. The results of major cytology studies using these methods of specimen collection are reported in *Table 3*. The reported sensitivity of cytological analysis of pure pancreatic juice for diagnosis of pancreatic cancer ranged from 54 to 76 per cent. The sensitivity of bile cytology in the diagnosis of malignancy in patients with biliary stricture varied from 30 to 73 per cent. This wide range is likely to result from differences in the groups of patients under investigation and in the methods of sampling for cytology. For example, samples of pancreatic juice were all obtained at the time of endoscopic pancreatography but some studies involved patients known to have pancreatic tumour[21] while others involved those undergoing diagnostic ERCP[22].

Over the past 10 years several studies have concentrated on bile exfoliative cytology in patients with obstructive jaundice caused by biliary stricture[26–31] (*Table 3*). Analysing the combined results from the six major studies reported since 1981 provides data on 236 patients and gives an overall sensitivity for exfoliative bile cytology of 38 per cent. Surprisingly, the overall sensitivity for duodenal aspirate cytology was superior to that for bile exfoliative cytology (58 *versus* 38 per cent; $\chi^2 = 23$, 1 d.f., $P < 0{\cdot}001$). This may reflect an earlier stage of disease currently being investigated. The most important aspect of the studies, on both pancreatic juice and bile, summarized in *Table 3* is the absence of false-positive results, resulting in a specificity of 100 per cent. A lack of false-positive results is of importance for any diagnostic test but is of particular significance when dealing with biliary stricture for which the treatment options are diverse and may be associated with considerable morbidity and mortality. The absolute specificity is generally attributed to obtaining a better sample for cytology by avoiding the degenerative changes that occur with cells exfoliated into the duodenum. The majority of studies on bile cytology reported in *Table 3* involved collection of samples endoscopically. Similar levels of sensitivity were found with percutaneous sampling, although the patient groups were generally different and direct comparison is not valid. Saline irrigation at PTC has been used to improve the results of percutaneous bile cytology. Iitsuka and colleagues[32] reported a sensitivity of 49 per cent in 55 patients with biliary stricture. Similar results were obtained in series where irrigation was not used, suggesting that this technique has no clear advantage. In some of the studies cited in *Tables 2* and *3* pancreatic secretion was stimulated with secretin or magnesium sulphate in an attempt to increase the number of exfoliated cells[13,16,21,33] The flow of pancreatic juice is undoubtedly enhanced by such means although a beneficial effect on the results of cytology has not been demonstrated.

Endobiliary brush cytology

Osnes *et al.*[34] first reported obtaining a cytological sample from the biliary tree endoscopically using a brush and shortly afterwards Mendez and colleagues[35] described the percutaneous

Table 3 *Exfoliative cytology on pancreatic juice and bile obtained at endoscopic retrograde cholangiopancreatography or percutaneous transhepatic cholangiography*

Reference	Year	No. of patients	Patients with cancer	True positive	False positive	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall accuracy (%)
Pancreatic juice cytology										
Endo *et al.*[21]	1974	29	29	22	n.a.	76	100	n.a.	n.a.	76
Hatfield *et al.*[22]	1976	61	26	14	0	54	100	100	74	80
Harada *et al.*[23]	1977	56	56	38	n.a.	68	n.a.	100	n.a.	68
Smithies *et al.*[24]	1977	61	26	17	0	65	100	100	80	85
Roberts-Thomson and Hobbs[25]	1979	33	17	10	0	59	100	100	70	79
Total		240	154	101	0	66	100	100	62	78
Bile cytology										
Harell *et al.*[26]	1981	19	15	7	0	47	100	100	33	58
Cobb and Floyd[27]	1985	18	12	6	0	50	100	100	50	66
Cohan *et al.*[28]	1985	38	32	14	0	44	100	100	25	53
Dalton-Clarke *et al.*[29]	1986	19	15	11	0	73	100	100	50	79
Desa *et al.*[30]	1991	80	64	19	0	30	100	100	26	44
Davidson *et al.*[31]	1992	62	47	14	0	30	100	100	31	47
Total		236	185	71	0	38	100	100	31	52

n.a., Data not available

Table 4 *Brush cytology*

Reference	Year	No. of patients	Patients with cancer	True positive	False positive	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall accuracy (%)
Pugliese *et al.*[36]	1987	22	12	8	0	66	n.a.	100	n.a.	82
Foutch *et al.*[37]	1989	9	7	4	0	57	100	100	40	66
Foutch *et al.*[38]	1990	39	24	13	0	54	100	100	58	72
Scudera *et al.*[39]	1990	25	20	12	0	60	100	100	39	68
Rabinovitz *et al.*[40]	1990	65	37	23	0	62	100	100	66	79
Desa *et al.*[30]	1991	24	10	5	1	50	93	83	74	76
Total		184	110	65	1	59	99	98	62	75

n.a., Data not available

Table 5 *Sensitivity of cytology for carcinoma of the pancreas and cholangiocarcinoma*

Reference	Year	Method	Carcinoma of pancreas	Cholangiocarcinoma
Harell *et al.*[26]	1981	Bile	3 of 5 (60)	2 of 6 (33)
Iitsuka *et al.*[32]	1984	Bile	5 of 17 (29)	22 of 27 (81)
Cobb and Floyd[27]	1985	Bile	1 of 6 (17)	3 of 5 (60)
Rupp *et al.*[10]	1990	Brush	21 of 23 (91)	6 of 6 (100)
Scudera *et al.*[39]	1990	Brush	5 of 10 (50)	2 of 2 (100)
Foutch *et al.*[38]	1990	Brush	4 of 7 (57)	6 of 6 (100)
Total			39 of 68 (57)	41 of 52 (79)

Values in parentheses are percentages

use of a cytology brush. However, it is only recently that endobiliary brush cytology has been studied closely. Data from the major studies are shown in *Table 4*. Results from a total of 184 patients have been reported, of whom 110 had cancer. The mean sensitivity is 59 per cent. Sensitivities reported for brush cytology range from 50 to 66 per cent, with the majority of studies yielding a similar overall sensitivity of 60 per cent. This range is narrow compared with that for exfoliative bile cytology from ERCP or PTC sampling (30–73 per cent; *Table 3*) and the mean overall sensitivity is also higher (59 *versus* 38 per cent). Comparing the true-positive results of brush cytology for biliary stricture with those of exfoliative bile cytology shows that the former are significantly better ($\chi^2 = 12$, 1 d.f., $P < 0{\cdot}001$). The more consistent sensitivity reported using brush cytology may be because the samples obtained are generally more cellular and therefore better suited for cytological diagnosis. As with exfoliative cytology on samples taken at ERCP or PTC, the specificity of brush cytology is excellent; only one false-positive result was reported with this technique[30]. In another study involving percutaneous sampling using both a reverse-screw device and a cytology brush another false-positive result occurred, but the cytologist was not aware of previous instrumentation on the bile duct, which may have led to misinterpretation[10].

Two published prospective controlled studies have compared bile and brush cytology for biliary stricture. Foutch and colleagues[41] studied 30 patients with biliary stricture of whom 17 had malignant lesions. Cytological analysis was positive in six of 18 biliary brushings but in only one of 18 bile samples. Although brush cytology appears to be significantly better, the results for both techniques were considerably poorer than those generally reported (*Tables 3* and *4*) and the difference was not statistically significant (Yates' $\chi^2 = 3$, 1 d.f., $P = 0{\cdot}1$–$0{\cdot}05$). Kurzawinski and colleagues[42] prospectively compared bile and brush cytology in 32 patients of whom 29 had malignant lesions. In this study the sensitivity of brush cytology was significantly greater than that of bile cytology at 59 *versus* 24 per cent ($\chi^2 = 7{\cdot}2$, 1 d.f., $P < 0{\cdot}01$), as was the diagnostic accuracy at 63 *versus* 31 per cent ($\chi^2 = 6{\cdot}3$, 1 d.f., $P = 0{\cdot}01$).

The sensitivity of bile or brush biliary cytology has generally been shown to be greater in patients with cholangiocarcinoma than in those with pancreatic cancer, although the number of patients studied is small (*Table 5*). Rabinovitz and colleagues[40] showed that the sensitivity of brush cytology increases with repeated brushings and that the probability of having bile duct cancer after three negative brushings is <6 per cent. However, repeated endobiliary brushing is time consuming and may predispose to biliary tract sepsis. Cytology brushes are effective because they enhance the exfoliation of tumour cells, giving more cells for assessment. Although this reduces the number of unsatisfactory samples, neoplasms not present on or infiltrating the mucosal lining of the bile duct will not be detected.

A major difficulty originally encountered with endobiliary brush cytology was that it required removal of the guidewire which had been negotiated across the stricture before brushing, which resulted in an often difficult reinsertion of the guidewire before stenting. The problem was largely overcome in 1989 by Foutch *et al.*[37], who described a novel method of introducing a cytology brush into the biliary tract along a guidewire that remained across the stricture. A small hole is made near the tip of the catheter which is fed along the guidewire that passes through the stricture. When the catheter reaches the site of the stricture a 6-Fr brush is passed through the catheter lumen and used to brush the stricture site. The superior results reported for brush cytology over exfoliative bile cytology seem likely to make it a first-line investigation for bile duct stricture.

There are several possible explanations for the results of biliary cytology being negative when a malignant biliary stricture is present. Metastatic carcinoma, lymphoma in periductal nodes or hepatocellular carcinoma without mucosal ulceration may produce biliary stricture by external compression. Difficulties may arise with cytology in pancreatic cancer related to enzymatic digestion and degeneration of exfoliated malignant cells[27]. Cholangiocarcinoma is usually fibrotic and its submucosal ductal growth occurs without significant ulceration and exfoliation. Pancreatic islet cell tumours do not communicate with the pancreatic duct and so cannot be

Table 6 *Endobiliary biopsy for biliary stricture*

Reference	Year	No. of patients	Patients with cancer	True positive	False positive	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall accuracy (%)
Aabakken *et al.*[45]	1986	17	10	3	0	30	100	100	50	59
Pugliese *et al.*[36]	1987	7	7	6	n.a.	86	100	100	n.a.	86
Rustgi *et al.*[46]	1989	5	5	4	n.a.	80	100	100	n.a.	80
Terasaki *et al.*[47]	1991	6	6	6	n.a.	100	100	100	n.a.	100
Total		35	28	19	0	68	100	100	44	74

n.a., Data not available

detected by exfoliative methods[21]. Although all of these reasons for negative cytology have been proposed, there is little evidence regarding their individual significance.

Endobiliary biopsy forceps

In an attempt to improve the diagnostic accuracy of cytology still further, an endobiliary biopsy forceps has been developed. Although the specimens may be suitable for either histological or cytological assessment, the amount of tissue obtained is usually small and so best suited for cytology. In 1978, Palayew and Stein[43] were the first to report endobiliary biopsy using a forceps, which was introduced via a T tube. Shortly after this, Elyaderani and Gabriele[44] reported the percutaneous use of a biopsy forceps and successful endobiliary biopsies have since been carried out both endoscopically and percutaneously. The few published series have usually involved small numbers of patients but suggest this technique to be highly sensitive, especially for diagnosing cholangiocarcinoma (*Table 6*). It has occasionally been possible to remove specimens 1–2 mm thick by this method, allowing tissue to be obtained even from extramucosal lesions[47]. Theoretical objections to the technique, namely bleeding or perforation, have not been substantiated[45,46,48].

Standard endoscopic biopsy forceps, designed for removing biopsy specimens from the duodenum, are too big to insert into the biliary tract without endoscopic sphincterotomy. This procedure is associated with small but significant morbidity and mortality rates[49] and a standard forceps is rarely used. A specially designed endobiliary forceps is now commercially available which is narrower and may be used without a sphincterotomy. Lesions on the side wall rather than in front of the forceps jaws are difficult to biopsy satisfactorily and the equipment presently available for endobiliary biopsy requires further refinement to ensure its routine use. However, for patients with suspected biliary malignancy and negative results from exfoliative bile and brush cytology, endobiliary biopsy should be considered as a second line of investigation.

Percutaneous fine-needle aspiration cytology

FNAC involves the analysis of cells sampled using a fine-bore needle either during open surgery or percutaneously, guided by imaging. The technique was introduced in Europe and America in the early 1930s[50,51] but found its place in the diagnosis of a variety of different cancers only in the 1970s[8]. The first percutaneous aspiration cytology of the pancreas was reported by Oscarson *et al.*[52] in 1972 and of the biliary tract by Evander and colleagues[53] in 1978. There are many high-resolution imaging techniques available for guiding the aspiration needle, but the most popular[54] is ultrasonography, which allows real-time visualization of lesions, is non-invasive and cheap. Other available methods include CT, fluoroscopy and angiography[29,53,55]. The main limitation of FNAC is that a mass lesion must be demonstrated by imaging before biopsy can be performed; this occurs in only two of every three patients with bile duct stricture[1]. Combining imaging methods such as ultrasonography and fluoroscopy may improve results[55]. Successful aspiration requires much practice and patience, and the accuracy of FNAC depends to a great extent on the ability of the clinician to obtain an adequate sample[53].

Aspiration is usually performed with a needle of outer diameter $\leqslant 1$ mm (19 G) which is passed through the lesion four to six times while applying gentle suction using a disposable syringe[56,57]. It is quite different from core or Tru-Cut (Travenol Laboratories, Thetford, UK) biopsies and is safer than other forms of abdominal biopsy. Smith[58] and Livraghi *et al.*[59] reported complication rates for abdominal FNAC of 0·16 and 0·55 per cent, respectively, and mortality rates of 0·006 and 0·008 per cent. If multiple passages of the needle are used in an attempt to improve diagnostic accuracy, the risk of haemorrhage, biliary peritonitis, bowel perforation or pancreatitis increases[58,59]. Tumour seeding has been observed, but only three definite cases were found following 63 108 procedures, an incidence of 0·005 per cent[58–61] or approximately 1 in 20 000. Despite this low incidence, it has been stated[62] that intraperitoneal dissemination of malignant cells from cancer of the pancreas is more common in patients who have undergone percutaneous FNAC and some surgeons consider such aspiration of potentially resectable tumours to be contraindicated. Seeding is more common when large-bore or biopsy needles are used[56].

The results of FNAC for biliary and pancreatic lesions in general are inferior to those for other tumours[63]. There is a large variation, from 42 to 67 per cent, in the reported sensitivity of FNAC for investigating biliary tumours (*Table 7*), which perhaps results from its dependence on operator skill and experience. Although about 50 per cent of patients were diagnosed successfully by FNAC, this figure overestimates its usefulness as these retrospective studies excluded many patients with biliary tumours who underwent imaging but were considered unsuitable for FNAC because of the absence of a visible focal lesion.

A comparison of percutaneous FNAC (*Table 7*) with brush cytology (*Table 5*) in patients with cholangiocarcinoma suggests that the latter may be the preferred initial method of diagnosis. This contrasts with the situation for pancreatic carcinoma (*Table 8*), which is commonly associated with a visible mass on imaging and in which the results of FNAC, with a mean sensitivity of 74 per cent, are generally better than those for brush cytology (*Table 5*). The main difficulty in diagnosing patients presenting with obstructive jaundice caused by a pancreatic mass is differentiating pancreatic carcinoma from chronic pancreatitis. Although the history and clinical findings may be helpful, diagnosis depends on obtaining histological or cytological confirmation. Unfortunately, this distinction may be difficult with both standard needle biopsies and FNAC as tissue in chronic pancreatitis often shows some characteristics of malignancy[8].

Intraoperative fine-needle aspiration cytology

Despite making every effort to establish a diagnosis before operation, surgery may have to be performed on patients with

Table 7 *Percutaneous fine-needle aspiration cytology in the diagnosis of bile duct tumours*

Reference	Year	No. of patients	Patients with cancer	True positive	False positive	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall accuracy (%)
Evander *et al.*[64]	1980	33	33	14	n.a.	42	n.a.	100	n.a.	42
Chitwood *et al.*[11]	1982	12	12	8	n.a.	67	n.a.	100	n.a.	67
Dalton-Clarke *et al.*[29]	1986	6	6	4	n.a.	67	100	100	n.a.	67
Hall-Craggs and Lees[55]	1986	32	30	17	0	57	100	100	13	59
Total		83	81	43	0	53	100	100	5	54

n.a., Data not available

Table 8 *Percutaneous fine-needle aspiration cytology in the diagnosis of a pancreatic mass*

Reference	Year	No. of patients	Patients with cancer	True positive	False positive	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall accuracy (%)
Tylen *et al.*[65]	1976	29	29	22	n.a.	76	n.a.	100	n.a.	76
Evander *et al.*[53]	1978	52	52	31	n.a.	60	n.a.	100	n.a.	60
Mitty *et al.*[66]	1981	53	43	37	0	86	100	100	63	89
Schwerk *et al.*[67]	1983	70	52	36	0	69	100	100	53	77
Hancke *et al.*[68]	1984	203	126	90	2	71	97	98	67	81
Holm *et al.*[69]	1985	190	117	84	2	72	97	98	68	82
Ekberg *et al.*[70]	1988	79	69	59	0	85	100	100	50	87
Total		676	488	359	4	74	98	99	59	80

n.a., Data not available

Table 9 *Intraoperative fine-needle aspiration cytology of a pancreatic mass*

Reference	Year	No. of patients	Patients with cancer	True positive	False positive	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Overall accuracy (%)
Forsgren and Orell[74]	1973	40	29	28	0	97	100	100	92	98
Ihse *et al.*[75]	1979	129	80	69	0	86	100	100	82	92
Keighley *et al.*[76]	1984	46	31	27	0	87	100	100	79	91
Smith *et al.*[77]	1985	31	25	19	0	76	100	100	50	81
Parson and Palmer[78]	1989	30	20	13	0	65	100	100	59	77
Hyoty *et al.*[79]	1991	98	50	35	0	70	100	100	76	85
Total		374	235	191	0	81	100	100	76	87

Unsatisfactory samples or those containing cells that were suspicious but not conclusive of malignancy have been considered negative

a biliary stricture of uncertain pathology. A mass in the liver, biliary tree or pancreas may also be an incidental finding at laparotomy. In these situations FNAC performed at laparotomy can be useful for obtaining a tissue diagnosis. It is safer than wedge, Tru-Cut or shave biopsies, which are associated with significant morbidity and mortality rates[71–73]. *Table 9* summarizes the findings of six major studies on the use of intraoperative FNAC for a pancreatic mass. No false-positive result has been encountered. The main difficulty with the technique is sampling error and, again, cytological differentiation between carcinoma of the pancreas and chronic pancreatitis. Choledochoscopy with lavage has also been used as a method for obtaining a diagnosis during surgery in patients with biliary stricture; Nishimura and colleagues[80] obtained a diagnosis of neoplasia in five of seven patients with cancer.

Endobiliary fine-needle aspiration cytology

Another method for obtaining a cytological sample of a biliary stricture is endobiliary FNA. This technique involves aspiration of tissue into a needle introduced through a catheter inserted either percutaneously[81] or endoscopically[82]. Thirty patients were investigated without complication by Cope and colleagues[81] using a 21- or 22-G Chiba needle through a standard percutaneous catheter; a diagnosis was obtained in 80 per cent of pancreatic cancers and 60 per cent of bile duct tumours. The authors reported that the procedure is time consuming and may not be possible for some distal bile duct strictures. For these, FNAC has been performed successfully both transduodenally and transgastrically, Tsuchiya *et al.*[83] reporting a sensitivity of 84 per cent with no false-positive result. Endoscopic techniques have been facilitated by the development of a special ball-tipped needle, use of which enabled a diagnosis to be made in 16 of 26 patients with biliary stricture[82]. The main attraction of endobiliary FNAC is its potential for diagnosing lesions that produce extrinsic compression of the biliary tree for which standard diagnostic methods have failed. Whether this potential will be realized has yet to be established.

Conclusions and future developments

The use of cytology for diagnosing the nature of a biliary tract stricture has been reviewed. Initial attempts at diagnosis using samples aspirated from the duodenum were sensitive but time consuming, associated with false-positive results, and did not allow the site of malignancy to be established. Over the past 20 years, bile aspiration for cytology with sampling at ERCP or PTC has allowed a diagnosis to be made in about one-third of malignancies of the pancreas or biliary tree; this test is remarkably safe and highly specific. The more recent development of biliary brush cytology has produced results that have been shown to be better than those of exfoliative bile cytology in two comparative studies. An endobiliary biopsy forceps has recently been developed and may allow lesions producing extrinsic compression on the biliary tree to be sampled safely. Results with such instruments are preliminary. The endobiliary aspiration cytology needle may also allow lesions that do not ulcerate the biliary mucosa to be diagnosed but, again, the data on this technique are preliminary. A diagnostic role will probably be established for both these techniques in patients with strictures for which simpler methods have failed. The main alternative to endobiliary cytology methods is percutaneous FNAC. This procedure is also remarkably safe and allows a diagnosis to be made in about 50 per cent of patients presenting with obstructive jaundice and in whom a mass lesion can be demonstrated by imaging. While it is beneficial to establish a diagnosis either before or without surgery, if all available methods have failed intraoperative cytology will establish the nature of a mass lesion in about 80 per cent of cases.

The main future developments required in the field of biliary cytology are techniques to facilitate cell sampling and methods for microscopic assessment of cytological samples. Improved imaging and instruments for tissue sampling will provide more cellular specimens but the problem of differentiating neoplastic from inflammatory changes remains. It is in this area and in the evaluation of patients with conditions that predispose to biliary malignancy, such as primary sclerosing cholangitis, that advances are likely to be made in cytological diagnosis[84]. Immunohistochemical and molecular techniques may evaluate the presence of tumour-associated antigens or oncogene products in exfoliated malignant cells. Such methods may give prognostic and, perhaps, diagnostic information such that patients at high risk of biliary malignancy may be detected[64,66–87].

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References

1. Baron RL, Stanley RJ, Lee JKT *et al.* Prospective comparison of the evaluation of biliary obstruction using computed tomography and ultrasonography. *Radiology* 1982; **145**: 91–8.
2. Wetter LA, Pellegrini CA, Way LW. Differential diagnosis of Klatskin tumours: preoperative diagnosis is often incorrect. *HPB Surg* 1990; **2**(Suppl): 119 (Abstract).
3. Wetter LA, Ring EJ, Pellegrini CA, Way LW. Differential diagnosis of sclerosing cholangiocarcinomas of the common hepatic duct (Klatskin tumor). *Am J Surg* 1991; **161**: 57–63.
4. Klintmalm GB, Stone MJ. Liver transplantation for malignancy. *Transplantation Reviews* 1990; **4**: 52–8.
5. Vecchio TJ. Predictive value of a single diagnostic test in unselected populations. *N Engl J Med* 1966; **274**: 1171–3.
6. Kassirer JP. Clinical trials and meta-analysis. What do they do for us? *N Engl J Med* 1992; **327**: 273–4.
7. Webb AJ. The role of cytology in surgical practice. *Current Practice in Surgery* 1991; 3: 27–33.
8. Koss LG. *Diagnostic Cytology and its Histopathologic Basis.* Philadelphia, Pennsylvania: JB Lippincott, 1979.
9. Bamforth J. *Cytological Diagnosis in Medical Practice.* London: Churchill, 1966.
10. Rupp M, Hawthorne CM, Ehya H. Brushing cytology in biliary tract obstruction. *Acta Cytol* 1990; **34**: 221–6.
11. Chitwood WR, Meyers WC, Heaston DK, Herskovic AM, McLeod ME, Jones RS. Diagnosis and treatment of primary extrahepatic bile duct tumors. *Am J Surg* 1982; **143**: 99–106.
12. Lemon HM, Byrnes WW. Cancer of the biliary tract and pancreas. *JAMA* 1949; **141**: 254–7.
13. Raskin HF, Wenger J, Sklar M, Pleticka BS, Yarema W. The diagnosis of cancer of the pancreas, biliary tract, and duodenum by combined cytologic and secretory methods. *Gastroenterology* 1958; **34**: 996–1017.
14. Raskin HF, Kirsner JB, Palmer WL. Role of exfoliative cytology in the diagnosis of cancer of the digestive tract. *JAMA* 1959; **169**: 789–91.
15. Bowden L, Papanicolaou GN. The diagnosis of pancreatic cancer by cytologic study of duodenal secretions. *Acta Unio International de Cancer* 1960; **16**: 398–404.
16. Dreiling DA, Nieburgs HE, Janowitz HD. The combined secretin and cytology test in diagnosis of pancreatic and biliary tract cancer. *Cancer Medicine Clinics of North America* 1960; **44**: 801–15.
17. Nieburgs HE, Dreiling DA, Rubio C, Reisman H. The morphology of cells in duodenal drainage smears: histologic origin and pathologic significance. *American Journal of Digestive Diseases* 1962; 7: 489–505.
18. Goldstein H, Ventzke LE, Wernett C. Value of exfoliative cytology in pancreatic carcinoma. *Gut* 1968; **9**: 316–18.
19. Prolla JC, Kirsner JB. *Handbook and Atlas of Gastrointestinal Exfoliative Cytology.* Chicago, Illinois: University of Chicago Press, 1972.
20. Kline TS, Joshi LP, Goldstein F. Preoperative diagnosis of pancreatic malignancy by the cytologic examination of duodenal secretions. *Am J Clin Pathol* 1978; **70**: 851–4.
21. Endo Y, Morii T, Tamura H, Okuda S. Cytodiagnosis of pancreatic malignant tumors by aspiration, under direct vision, using a duodenal fiberscope. *Gastroenterology* 1974; **67**: 944–51.
22. Hatfield ARW, Smithies A, Wilkins R, Levi AJ. Assessment of endoscopic retrograde cholangio-pancreatography (ERCP) and pure pancreatic juice cytology in patients with pancreatic disease. *Gut* 1976; **17**: 14–21.
23. Harada H, Sasaki T, Yamamoto N *et al.* Assessment of endoscopic aspiration cytology and endoscopic retrograde cholangio-pancreatography (ERCP) in patients with cancer of pancreas. Part I. *Gastroenterol Jpn* 1977; **12**: 52–8.
24. Smithies A, Hatfield AR, Brown BE. The cytodiagnostic aspects of pure pancreatic juice obtained at the time of endoscopic retrograde cholangio-pancreatography (ERCP). *Acta Cytol* 1977; **21**: 191–5.
25. Roberts-Thomson IC, Hobbs JB. Cytodiagnosis of pancreatic and biliary cancer by endoscopic duct aspiration. *Med J Aust* 1979; **1**: 370–2.
26. Harell GS, Anderson MF, Berry PF. Cytologic bile examination in the diagnosis of biliary duct neoplastic strictures. *AJR Am J Roentgenol* 1981; **137**: 1123–6.
27. Cobb CJ, Floyd WN. Usefulness of bile cytology in the diagnostic management of patients with biliary tract obstruction. *Acta Cytol* 1985; **29**: 93–100.
28. Cohan RH, Illescas FF, Newman GE, Braun SA. Biliary cytodiagnosis. Bile sampling for cytology. *Invest Radiol* 1985; **20**: 177–9.
29. Dalton-Clarke HJ, Pearse E, Krausz T, McPherson GAD, Benjamin IS, Blumgart LH. Fine needle aspiration cytology and exfoliative biliary cytology in the diagnosis of hilar cholangiocarcinoma. *Eur J Surg Oncol* 1986; **12**: 143–5.
30. Desa LA, Akosa AB, Lazzara S, Domizio P, Krausz T, Benjamin IS. Cytodiagnosis in the management of extrahepatic biliary strictures. *Gut* 1991; **32**: 1188–91.
31. Davidson BR, Varsamidakis N, Dooley JS *et al.* The value of exfoliative cytology for investigating bile duct strictures. *Gut* 1992; **33**: 1408–11.
32. Iitsuka Y, Hiraoka H, Kimura A, Kodoh H, Koga S. Diagnostic significance of bile cytology in obstructive jaundice. *Jpn J Surg* 1984; **14**: 207–11.
33. Wenger J, Raskin HF. The diagnosis of cancer of the pancreas, biliary tract and duodenum by combined cytologic and secretory methods: II. The secretin test. *Gastroenterology* 1958; **34**: 1009–17.
34. Osnes M, Serck-Hanssen A, Myren J. Endoscopic retrograde brush cytology (ERBC) of the biliary and pancreatic ducts. *Scand J Gastroenterol* 1975; **10**: 829–31.
35. Mendez A Jr, Russel E, Levi JU, Koolpe H, Cohen M. Percutaneous brush biopsy and internal drainage of biliary tree through endoprosthesis. *American Journal of Radiology* 1980; **134**: 653–9.
36. Pugliese V, Barone D, Saccomanno S, Conio M, Aste H, Santi L. Tissue sampling from the common bile duct through endoscopic

retrograde cholangiopancreatography, endoscopic papillo(sphinctero)tomy and drainage in juxtapapillary malignancies. *Surg Endosc* 1987; **1**: 83–7.

37. Foutch PG, Harlan JR, Kerr D, Sanowski RA. Wire-guided brush cytology: a new endoscopic method for diagnosis of bile duct cancer. *Gastrointest Endosc* 1989; **35**: 243–7.
38. Foutch PG, Kerr DM, Harlan JR, Manne RK, Kummet TD, Sanowski RA. Endoscopic retrograde wire-guided brush cytology for diagnosis of patients with malignant obstruction of the bile duct. *Am J Gastroenterol* 1990; **85**: 791–5.
39. Scudera PL, Koizumi J, Jacobson IM. Brush cytology evaluation of lesions encountered during ERCP. *Gastrointest Endosc* 1990; **36**: 281–4.
40. Rabinovitz M, Zajko AB, Hassanein T *et al.* Diagnostic value of brush cytology in the diagnosis of bile duct carcinoma: a study in 65 patients with bile duct strictures. *Hepatology* 1990; **12**: 747–52.
41. Foutch PG, Kerr DM, Harlan JR, Kummet TD. A prospective, controlled analysis of endoscopic cytodiagnosis for diagnosis of malignant biliary stricture. *Am J Gastroenterol* 1991; **86**: 557–80.
42. Kurzawinski TR, Deery A, Dooley JS, Dick R, Hobbs KEF, Davidson BR. A prospective study comparing brush and bile exfoliative cytology for diagnosing bile duct strictures. *Gut* 1992; **33**: 1675–7.
43. Palayew MJ, Stein L. Postoperative biopsy of the common bile duct via the T tube tract. *AJR Am J Roentgenol* 1978; **130**: 287–9.
44. Elyaderani MK, Gabriele OF. Brush and forceps biopsy of biliary ducts via percutaneous transhepatic catheterization. *Radiology* 1980; **135**: 777–8.
45. Aabakken L, Karesen R, Serck-Hanssen A, Osnes M. Transpapillary biopsies and brush cytology from the common bile duct. *Endoscopy* 1986; **18**: 49–51.
46. Rustgi AK, Kelsey PB, Guelrud M, Saini S, Schapiro RH. Malignant tumors of the bile ducts: diagnosis by biopsy during endoscopic cannulation. *Gastrointest Endosc* 1989; **35**: 248–51.
47. Terasaki K, Wittich GR, Lycke G *et al.* Percutaneous transluminal biopsy of biliary strictures with a bioptome. *AJR Am J Roentgenol* 1991; **156**: 77–8.
48. Dancygier H. Endoscopic transpapillary biopsy (ETPB) of human extrahepatic bile ducts – light and electron microscopic findings, clinical significance. *Endoscopy* 1989; **21**(Suppl 1): 312–20.
49. Cotton PB. Endoscopic management of bile duct stones; (apples and oranges). *Gut* 1984; **25**: 587–97.
50. Martin HE, Ellis EB. Aspiration biopsy. *Surg Gynecol Obstet* 1934; **59**: 578–89.
51. Frola E. Etude clinique de l'état functionnel du foie par la ponction hèpatique. *Presse Med* 1935; **43**: 323–30.
52. Oscarson J, Stormby N, Sundgren N. Selective angiography in fine needle aspiration cytodiagnosis of gastric and pancreatic tumours. *Acta Radiol* 1972; **12**: 737–49.
53. Evander A, Ihse I, Lunderquist A, Tylen U, Akerman M. Percutaneous cytodiagnosis of carcinoma of the pancreas and bile duct. *Ann Surg* 1978; **188**: 90–2.
54. Lees WR. Pancreatic ultrasonography. *Baillieres Clin Gastroenterol* 1984; **13**: 763–89.
55. Hall-Craggs MA, Lees WR. Fine needle aspiration biopsy: pancreatic and biliary tumors. *AJR Am J Roentgenol* 1986; **147**: 399–403.
56. Soreide O. Percutaneous aspiration cytology. In: Blumgart LH, ed. *Surgery of the Liver and Biliary Tract.* Vol. 1. New York: Churchill Livingstone, 1990: 327–35.
57. Red DE. Imaging modalities for biopsy assistance. In: Kline TS, ed. *Handbook of Fine Needle Aspiration Biopsy Cytology.* St Louis, Missouri: Mosby, 1981: 8–22.
58. Smith EH. The hazards of fine needle aspiration biopsy. *Ultrasound Med Biol* 1984; **10**: 629–34.
59. Livraghi T, Damascelli B, Lombardi C, Spagnoli I. Risk in fine needle aspiration biopsy. *JCU J Clin Ultrasound* 1983; **11**: 77–81.
60. Ferruci JT, Wittenberg J, Margolies NM, Carey RW. Malignant seeding of the tract after thin needle aspiration biopsy. *Radiology* 1979; **130**: 345–6.
61. Smith FP, McDonald JS, Schein PS, Ornitz RD. Cutaneous seeding of pancreatic cancer by skinny needle aspiration biopsy. *Arch Intern Med* 1980; **140**: 855.
62. Warshaw LA. Implications of peritoneal cytology for staging of early pancreatic cancer. *Am J Surg* 1991; **161**: 26–30.
63. Steinberg W. The clinical utility of the CA19-9 tumor-associated antigen. *Am J Gastroenterol* 1990; **85**: 350–5.
64. Evander A, Fredlund P, Hoevels J, Ihse I, Bengmark S. Evaluation of aggressive surgery for carcinoma of the extrahepatic bile ducts. *Ann Surg* 1980; **191**: 23–9.
65. Tylen U, Arnesjo B, Lindberg RG, Lunderquist A, Akerman M. Percutaneous biopsy of carcinoma of the pancreas guided by angiography. *Surg Gynecol Obstet* 1976; **142**: 737–9.
66. Mitty HA, Efremidis SC, Yeh HC. Impact of fine-needle biopsy on management of patients with carcinoma of the pancreas. *AJR Am J Roentgenol* 1981; **137**: 1119–21.
67. Schwerk WB, Durr HK, Schmitz-Moormann P. Ultrasound guided fine-needle biopsies in pancreatic and hepatic neoplasms. *Gastrointest Radiol* 1983; **8**: 219–25.
68. Hancke S, Holm HH, Koch F. Ultrasonically guided puncture of solid pancreatic mass lesions. *Ultrasound Med Biol* 1984; **19**: 613–15.
69. Holm HH, Torp-Pedersen S, Larsen T, Juul N. Percutaneous fine needle biopsy. *Baillieres Clin Gastroenterol* 1985; **14**: 423–49.
70. Ekberg O, Bergenfeldt M, Aspelin P *et al.* Reliability of ultrasound-guided fine-needle biopsy of pancreatic masses. *Acta Radiol* 1988; **29**: 535–9.
71. Lightwood R, Reber HA, Way LW. The risk and accuracy of pancreatic biopsy. *Am J Surg* 1976; **132**: 189–94.
72. Simms MH, Tindall N, Allan RN. Pancreatic fistula following operative fine needle aspiration. *Br J Surg* 1982; **69**: 548.
73. Rosenbaum DA, Frost DB. Fine needle aspiration biopsy of the pancreas complicated by pancreatic ascites. *Cancer* 1990; **65**: 2537–8.
74. Forsgren L, Orell S. Aspiration cytology in carcinoma of the pancreas. *Surgery* 1973; **73**: 38–42.
75. Ihse I, Toregard BM, Akerman M. Intraoperative fine needle aspiration cytology in pancreatic lesions. *Ann Surg* 1979; **190**: 732–4.
76. Keighley MRB, Moore J, Thompson H. The place of fine needle aspiration cytology for the intraoperative diagnosis of pancreatic malignancy. *Ann R Coll Surg Engl* 1984; **66**: 405–8.
77. Smith RC, Lin BPC, Loughman NT. Operative fine needle aspiration cytology of pancreatic tumours. *Aust N Z J Surg* 1985; **55**: 145–8.
78. Parson L, Palmer CH. How accurate is fine needle biopsy in malignant neoplasia of the pancreas? *Arch Surg* 1989; **124**: 681–3.
79. Hyoty MK, Matilla JJ, Salo K, Nordback IH. Intraoperative fine needle aspiration cytologic examination of pancreatic lesions. *Surg Gynecol Obstet* 1991; **173**: 193–7.
80. Nishimura A, Den N, Sato H, Takeda B. Exfoliative cytology of the biliary tract with the use of saline irrigation under choledochoscopic control. *Ann Surg* 1973; **178**: 594–9.
81. Cope C, Marinelli DL, Weinstein JK. Transcatheter biopsy of lesions obstructing the bile ducts. *Radiology* 1988; **169**: 555–6.
82. Howell DA, Beveridge RP, Bosco J, Jones M. Endoscopic needle aspiration biopsy at ERCP in the diagnosis of biliary strictures. *Gastrointest Endosc* 1992; **38**: 531–5.
83. Tsuchiya R, Kenmi T, Kondo Y, Akashi M, Harada H. Endoscopic aspiration biopsy of the pancreas. *Gastroenterology* 1977; **73**: 1050–2.
84. Miros M, Kerlin P, Walker N, Lynch S, Strong R. Predicting cholangiocarcinoma in patients with primary sclerosing cholangitis before transplantation. *Gut* 1991; **32**: 1369–73.
85. Yamaguchi K, Enjoji M, Nakayama F. Cancer of the extrahepatic bile ducts: a clinicopathologic study of immunohistochemistry for CEA, CA19-9 and p21. *World J Surg* 1988; **12**: 11–17.
86. Davis RI, Sloan JM, Hood JM, Maxwell P. Carcinoma of the extrahepatic biliary tree: a clinicopathological and immunohistochemical study. *Histopathology* 1988; **12**: 623–31.
87. Hall PA, Ray A, Lemonie NR, Midgly CA, Krausz T, Lane DP. p53 immunostaining as a marker of malignant disease in diagnostic cytopathology. *Lancet* 1991; **338**: 513 (Letter).

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Review

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Adrenal incidentaloma

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Improvements in ultrasonography and computed tomography have led to the problem of 'adrenal incidentaloma', an asymptomatic adrenal mass discovered during investigation of some other problem. In the light of current knowledge a management rationale for patients with such an adrenal abnormality is proposed.

Improvements in the availability of high-resolution ultrasonography and computed tomography (CT) have led to the clinical problem of 'adrenal incidentaloma'[1]. This is an asymptomatic adrenal mass discovered during the course of investigation of an unrelated condition. Data are reviewed on which a rational management for such lesions might be based.

Prevalence

Hedeland and colleagues[2] in 1968 reported the results of a 20-year prospective study of 739 consecutive autopsies; 64 adrenocortical adenomas were discovered. During the 20-year period, 70 per cent of deaths within the city of Malmö in Sweden were followed by post-mortem examination. Patients below the age of 20 years were excluded but otherwise the material was unselected. The prevalence of adrenocortical adenoma was 8·7 per cent. A more recent retrospective study[3] of 1116 unselected consecutive autopsy reports of patients of 18 years or more described 73 adrenal glands with a grossly visible mass, a prevalence of 6·5 per cent. The prevalence of adrenal mass discovered by CT is somewhat less. This may reflect differences in the population examined by CT and that undergoing post-mortem examination, as well as the limits of resolution of scanning. In a study of 2200 patients, Glazer and colleagues[4] identified 16 with an adrenal mass by CT, a prevalence of 0·7 per cent. Abecassis *et al.*[3] in 1985 and Belldegrun and colleagues[5] described 19 of 1459 patients (1·3 per cent) and 88 of 12 000 (0·7 per cent), respectively, with an incidental adrenal mass discovered by CT. It would appear, therefore, that the prevalence of adrenal incidentaloma discovered by abdominal CT is at present around 1–2 per cent; this may increase with improvements in the resolution of scanning.

Pathology

The clinical importance of adrenal incidentalomas depends on their pathology; they may represent both malignant and functional tumours but also abnormalities that do not require resection. Simple adrenal cyst, adenolipoma and adrenal haematoma can usually be identified by CT alone[6]. Primary adrenal carcinoma is a rare condition. Reviewing 171 adrenal incidentalomas[3–5,7–11], only eight (4·7 per cent) were primary carcinoma. Metastatic adrenal carcinoma is extremely uncommon in the absence of an obvious primary lesion. Of 171 incidental adrenal masses, seven (4·1 per cent) were metastases with no obvious primary malignant condition. In contrast, of 988 autopsy reports describing the adrenal gland, 73 glands were found to have a pathological abnormality of which 50 (68 per cent) were metastases, although most of the patients were already known to be suffering from malignant disease[3]. Of the remaining 23 adrenal glands with a pathological abnormality, 19 were cortical adenoma, two myelolipoma, one a haematoma and one a phaeochromocytoma. However, excluding metastatic malignant disease, most adrenal masses at autopsy proved to be benign cortical adenoma. This is also true of adrenal incidentaloma. Of 171 incidentalomas described[3–5,7–11], 44 (25·7 per cent) proved to be cortical adenoma, only one of which was functioning (Cushing's syndrome). One adrenal incidentaloma was found to be a phaeochromocytoma and was associated with firm biochemical evidence of catecholamine excess.

Among patients known to have a malignancy, metastasis is the most common cause of an incidental adrenal mass. Belldegrun *et al.*[5] described 33 patients with a known malignancy in association with an adrenal mass of whom 24 were found to have an adrenal metastasis. Katz and Shirkhoda[12] described 16 patients with a non-functioning adrenal mass in association with a variety of primary extra-adrenal malignant neoplasms; nine proved to have an adrenal metastasis.

Management of adrenal incidentaloma depends first on whether there is an excess of adrenal hormone and second on distinguishing between benign and malignant (primary or secondary) adrenal masses.

Hormonal evaluation

Patients with simple adrenal cyst and adenolipoma, which can be identified by their characterstic appearance on CT, do not require evaluation to detect hormonal hypersecretion[6,13]. Other adrenal lesions, such as phaeochromocytoma, functioning adrenal carcinoma or adenoma, may be hormonally active producing an excess of glucocorticoids, mineralocorticoids or sex steroids.

Phaechromocytoma has a typical appearance on CT that suggests it as a likely diagnosis (*Figure 1*) and is usually visualized by isotopic scanning with *m*-iodobenzylguanidine. A detailed analysis of the evaluation of patients with an

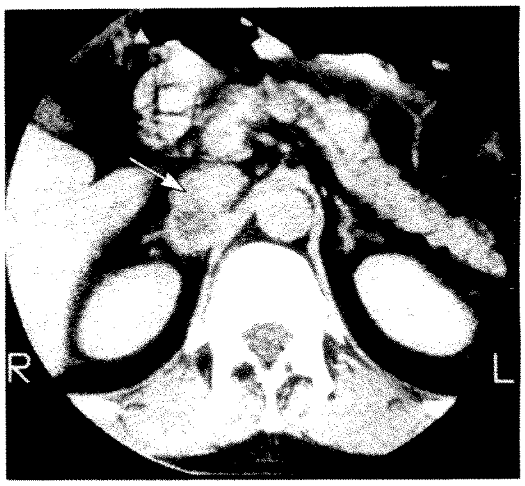

Figure 1 *Computed tomography showing small but typical phaeochromocytoma of the right adrenal gland with patchy enhancement (arrow). The normal left adrenal gland is readily seen as a curled leaf shape*

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incidentally discovered adrenal mass has been provided by Ross and Aron[13]. Based on a careful review of the literature, negative and positive predictive values were calculated for various clinical findings and screening tests in the evaluation of a patient with an adrenal mass. According to a large autopsy series of 40078 patients at the Mayo Clinic, the prevalence of phaeochromocytoma in a population of patients with an incidentally discovered adrenal mass should be 6·5 per cent[14]. Despite this low prevalence, phaeochromocytoma is a potentially lethal disorder with an unpredictable course and, therefore, the authors recommended that all patients with an incidentally discovered adrenal mass are screened for phaeochromocytoma. It was calculated that the negative predictive value of 24-h urinary vanillylmandelic acid excretion measurement is 98·2 per cent; the complete absence of symptoms and of hypertension raises the negative predictive value for the diagnosis of phaeochromocytoma to 99·6 per cent[13]. The positive predictive value of a single raised urinary vanillylmandelic acid excretion measurement is, however, substantially lower at 71·8 per cent and additional biochemical testing, such as the measurement of urinary or plasma catecholamine levels, is therefore required before surgery is considered.

Virtually all patients with primary hyperaldosteronism have hypertension at the time of diagnosis; if hypertension is absent, biochemical exclusion of the diagnosis is not required. Ross and Aron[13] calculated that the prevalence of aldosterone-producing adenoma in patients with an incidentally discovered adrenal mass is 7 per cent. The positive predictive value of spontaneous hypokalaemia for the diagnosis of aldosterone-producing adenoma in a hypertensive patient with an adrenal mass was calculated to be approximately 95 per cent. The authors recommended, therefore, that only hypertensive patients who have spontaneous hypokalaemia require specific measurement of plasma aldosterone levels.

Despite its 50-fold increased prevalence in patients with an incidentally discovered mass, glucocorticoid-producing adenoma is extremely rare. The probability that an incidental adrenal mass is an adrenal adenoma producing an excess of glucocorticoids is approximately 0·035 per cent[13]. In the absence of hypertension or obesity this probability falls to approximately 0·01 per cent[13]. Thus, glucocorticoid hypersecretion is extremely rare in the absence of bruising, striae, myopathy and the other stigmas of Cushing's syndrome.

Surgery is indicated for the few patients in whom an adrenal incidentaloma is associated with hormone hypersecretion.

Diagnostic imaging

Primary adrenal carcinoma is rare, with an annual incidence estimated to range from 0·06 to 0·27 per 100000 population[1]. In 1990, there were only 104 deaths from primary adrenal malignancy in England and Wales[15]. If it is assumed that the disease takes up to 7 years to become clinically apparent, the expected prevalence of primary adrenal carcinoma in a population of patients with an adrenal mass would be 58·3 per 100000, i.e. <0·06 per cent of all adrenal incidentalomas[1,13]. Using published data, Ross and Aron[13] calculated that, based on the size of a lesion detected by CT, fewer than 1 in 10000 lesions <6 cm in diameter would represent adrenal carcinoma, a negative predictive value >99·9 per cent. Thus it would appear that size alone is a sensitive screening criterion in the detection of adrenal carcinoma. Most carcinomas are large at presentation and have an unequivocal appearance on CT (*Figure 2*).

Features on CT other than size that may suggest malignancy are an irregular contour, invasion of adjacent structures and metastasis to retroperitoneal lymph nodes and distant organs[6,8], signs that are particularly important when diagnosing metastatic malignancy (*Figure 3*). Adrenal carcinoma may be rapidly growing and a rapid change in size observed on serial scan at 3-month intervals is an indicator of malignancy.

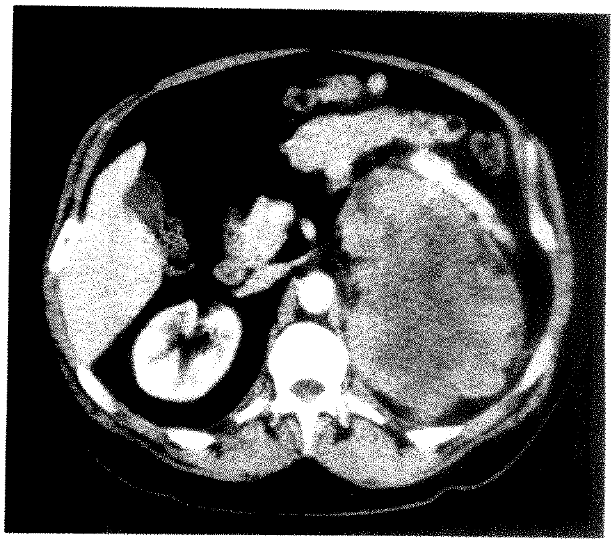

Figure 2 *Computed tomography showing a typical carcinoma of the adrenal gland with large size at presentation, irregular margins and invasion of surrounding structures. The example shown is a malignant adrenocortical carcinoma presenting as Cushing's syndrome in a 62-year-old man*

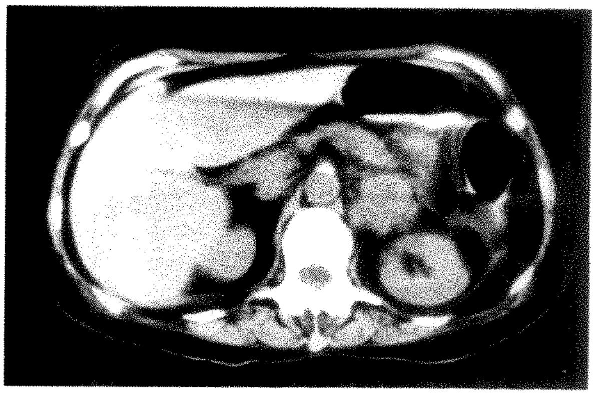

Figure 3 *Computed tomography showing metastatic lymphoma in the left adrenal gland. The irregular outline suggests malignancy. Enlarged lymph nodes were demonstrated on the same scan*

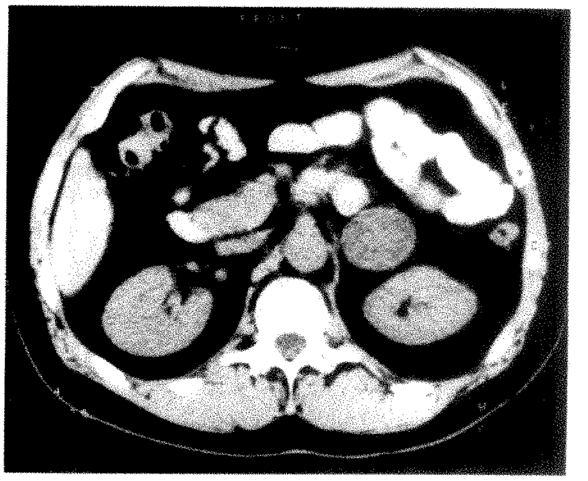

Figure 4 *Computed tomography showing benign adenoma of the left adrenal gland. The patient was shown to be suffering from Conn's syndrome. Although the tumour is larger than normally encountered in this condition, its outline is smooth and its consistency homogeneous. The lesion was benign on histological examination*

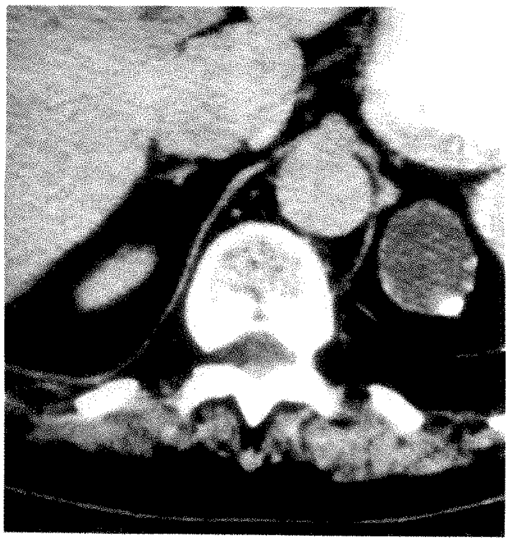

Figure 5 *Computed tomography showing a left adrenal cyst with some calcification in the wall*

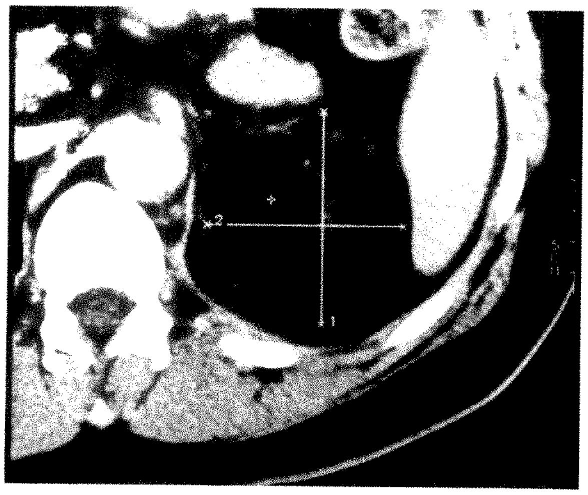

Figure 6 *Computed tomography showing myelolipoma of the left adrenal gland. Dark spaces are typical because of the high fat content of the tumour*

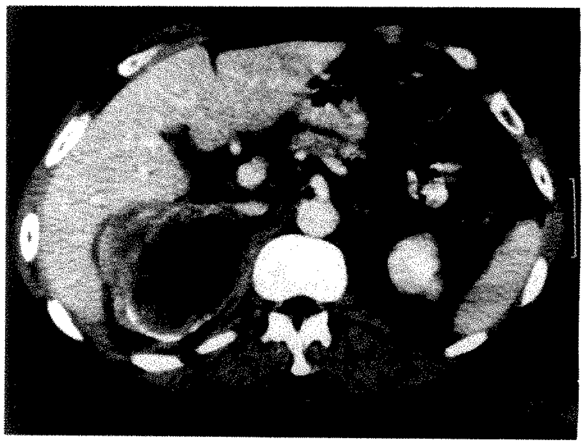

Figure 7 *Computed tomography showing haematoma of the right adrenal gland. Although calcified this was found on excision to result from haemorrhage into a metastasis from a carcinoma of the bronchus treated some years previously*

Nearly all solid lesions <6 cm in diameter are benign adenomas. They have a smooth contour, well defined margins and show no growth on serial CT (*Figure 4*). Cysts, myelolipoma and haematoma have a specific and characteristic appearance on CT (*Figures 5–7*).

Functional scintigraphy using [^{131}I]6-β-iodomethyl-19-norcholesterol (NP-59) in conjunction with CT can help differentiate a benign from a malignant adrenal mass[16–19]. Gross *et al.*[18] studied 119 patients with a unilateral adrenal mass discovered on CT. Increased uptake on the side shown to have the adrenal mass, i.e. concordant imaging, was associated with benign pathology. Seventy-six of the 82 adenomas in the series demonstrated concordant imaging. Asymmetric NP-59 uptake localizing to the side opposite the abnormal gland on the scan (discordant imaging) was demonstrated in 26 patients. These adrenal masses proved to be metastatic malignancy in 19 patients, primary adrenal neoplasm other than adenoma in four and an adrenal cyst in three. Concordant CT and radionuclide scanning virtually excluded malignant disease[20].

Magnetic resonance imaging (MRI) has a sensitivity comparable to that of CT in the detection of adrenal mass[21]. Early reports suggested that MRI may help with tissue characterization and distinguish benign from malignant lesions[22,23]. However, Khafagi and colleagues[24] described a group of 45 patients with large adrenal masses (>5 cm in diameter) and found neither CT nor MRI helpful in distinguishing benign from malignant.

Fine-needle aspiration biopsy

Berkman *et al.*[25] described a series of 16 patients with an adrenal mass who underwent percutaneous biopsy under CT guidance with 18–22-G needles. Using this technique, adrenal adenoma, cyst, metastasis, melanoma and adrenal haemorrhage were identified. There were no false-positive examinations or complications in this series. Heaston *et al.*[26] described a series of 14 patients who underwent CT-guided needle biopsy; diagnostic cytological specimens were obtained in 13. It was possible to diagnose primary and metastatic neoplasm in ten patients, benign adenoma in two and mycotic abscess in one. There were no false-positive diagnoses. Two patients thought to have adrenocortical carcinoma underwent surgery and the cytological diagnosis was confirmed by histological examination. Bernardino *et al.*[27] performed 58 percutaneous needle biopsies of adrenal masses in 53 patients under CT guidance and reported a correct tissue diagnosis from the initial biopsy in 83 per cent of patients. Four of the remaining nine patients underwent a second biopsy and an accurate diagnosis was obtained eventually for 48 of the 53 patients (91 per cent). Complications were noted in six of the 53 (11 per cent). There were seven minor complications (12 per cent) from 58 procedures, related mainly to blood loss requiring transfusion. Bernardino *et al.*[27] have recommended that percutaneous CT-guided needle biopsy is an acceptable alternative to open biopsy. Others have emphasized the limitations of needle biopsy, particularly in the diagnosis of primary adrenal carcinoma, which normally depends on the demonstration of capsular and vascular invasion.

Fine-needle aspiration biopsy may be of particular value in patients with a known extra-adrenal malignancy. Metastasis is a frequent cause of an incidental adrenal mass[5,12]. Fine-needle aspiration biopsy is simple and less invasive than adrenalectomy and can provide a histological diagnosis of the adrenal mass where this may influence management. It is not, therefore, appropriate when a hormonally active tumour has been identified and should not be employed when phaeochromocytoma is suspected.

Policy for managing adrenal incidentaloma

An unsuspected adrenal mass is detected in 1–2 per cent of abdominal CT examinations. Seddon and colleagues[11] advocated surgical exploration of all adrenal incidentalomas in view of the disparity observed between the clinical and final

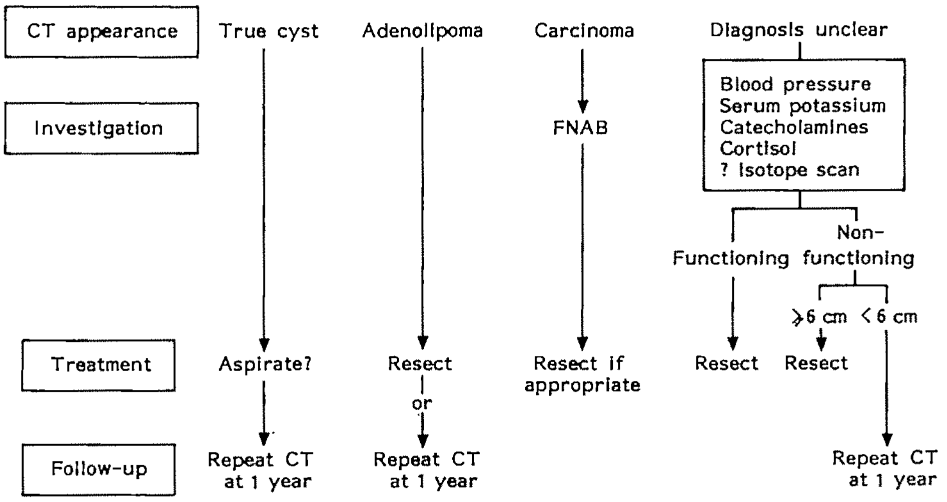

Figure 8 *Flow chart for management of adrenal incidentaloma. CT, computed tomography; FNAB, fine-needle aspiration biopsy*

histological diagnoses in a group of 11 patients with an adrenal mass, all of whom underwent surgical exploration. Malignancy was discovered in four patients. However, the size of the adrenal masses was not given and it is interesting to note that none of the four adrenal malignancies was amenable to surgical excision. A policy of exploring all adrenal incidentalomas has not found general acceptance. Management of the incidentaloma must be guided by the high prevalence of benign and clinically unimportant adrenal adenoma compared with the rarity of occult non-functioning adrenocortical carcinoma or functioning adenoma. The quest for diagnostic certainty must be tempered by the need to avoid iatrogenic complications[28].

The following policy for intervention (*Figure 8*) seems to fit safely within the framework of current knowledge:

1. Exclude benign lesions identified by CT. Adenolipoma and simple cyst have characteristic appearances on CT. Adrenal haemorrhage is not easily diagnosed by scanning as it may be mimicked by a phaeochromocytoma and, even when a haematoma is accurately diagnosed, may represent bleeding into an adrenal tumour.
2. Assess the size of the lesion by CT. The size at which an adrenal mass requires surgical exploration, or at least a histological diagnosis, has been variously described[1,3–5,8,13,29–31] as 2·5, 3, 3·5, 4, 5 and 6 cm. However, the negative predictive value for primary adrenal carcinoma in adrenal masses <6 cm in diameter is >99·9 per cent and there is little evidence to show that MRI, radionuclide imaging or percutaneous needle biopsy improves diagnostic accuracy without greatly increasing cost and morbidity. The potential benefit, as yet unproven, of early removal of the rare primary adrenal carcinoma must be balanced against the morbidity and mortality associated with surgery for the more common benign lesions. CT appearances suggestive of malignancy, such as irregular borders, local invasion and metastases, are indications for cytological or histological examination of smaller lesions. However, all adrenal masses ⩾6 cm in size require surgical exploration, with the exception of those in patients whose clinical history raises the possibility of adrenal metastasis. Fine-needle aspiration biopsy is an acceptable investigation in these patients if it is thought that the result might influence management.
3. Limited investigation of small lesions. Clinical assessment may point to a functioning adenoma but measurement of levels of serum cortisol and potassium, and urinary catecholamine or vanillylmandelic acid, are needed to exclude preclinical Cushing's syndrome, Conn's syndrome and phaechromocytoma. Once these are excluded, further investigation by, for example, needle sampling can be reserved for lesions noted to be enlarging on serial CT.

References

1. Copeland PM. The incidentally discovered adrenal mass. *Ann Intern Med* 1983; **98**: 940–5.
2. Hedeland H, Ostberg G, Hokfelt B. On the prevalence of adrenocortical adenomas in autopsy material in relation to hypertension and diabetes. *Acta Medica Scandinavica* 1968; **184**: 211–14.
3. Abecassis M, McLoughlin MJ, Langer B, Kudlow JE. Serendipitous adrenal masses: prevalence, significance and management. *Am J Surg* 1985; **149**: 783–8.
4. Glazer HS, Weyman PJ, Sagel SS, Levitt RG, McClennan BL. Nonfunctioning adrenal masses: incidental discovery on computed tomography. *AJR Am J Roentgenol* 1982; **139**: 81–5.
5. Belldegrun A, Hussain S, Seltzer SE, Loughlin KR, Gittes RF, Richie JP. Incidentally discovered mass of the adrenal gland. *Surg Gynecol Obstet* 1986; **163**: 203–8.
6. Moulton JS. CT of the adrenal glands. *Semin Roentgenol* 1988; **33**: 288–303.
7. Prinz RA, Brooks MH, Churchill R *et al.* Incidental asymptomatic adrenal masses detected by computed tomographic scanning: is operation required? *JAMA* 1982; **248**: 701–4.
8. Mitnick JS, Bosniak MA, Megibow AJ, Naidich DP. Non-functioning adrenal adenomas discovered incidentally on computed tomography. *Radiology* 1983; **148**: 495–9.
9. Geelhoed GW, Druy EM. Management of the adrenal 'incidentaloma'. *Surgery* 1982; **92**: 866–74.
10. Guerrero LA. Diagnostic and therapeutic approach to incidental adrenal mass. *Urology* 1985; **26**: 435–40.
11. Seddon MJ, Baranetsky N, Van Boxel PJ. Adrenal 'incidentalomas': need for surgery. *Urology* 1985; **25**: 1–7.
12. Katz RL, Shirkhoda A. Diagnostic approach to incidental adrenal nodules in the cancer patient. *Cancer* 1985; **55**: 1995–2000.
13. Ross NS, Aron DC. Hormonal evaluation of the patient with an incidentally discovered adrenal mass. *N Engl J Med* 1990; **323**: 1401–5.
14. Sutton MG, Sheps SG, Lie JT. Prevalence of clinically unsuspected pheochromocytoma: review of a 50-year autopsy series. *Mayo Clin Proc* 1981; **56**: 354–60.
15. Office of Population Censuses and Surveys. *Mortality Statistics – Cause*. Series DH2. No. 17. 1990. London: HMSO, 1991: 16.
16. Thrall JH, Freitas JE, Beierwaltes WH. Adrenal scintigraphy. *Semin Nucl Med* 1978; **8**: 23–41.
17. Quraishi MA, Costanzi JJ, Balachandran S. Iodocholesterol adrenal scanning for the detection of adrenal metastases in lung cancer and its clinical significance. *Cancer* 1981; **48**: 714–16.
18. Gross MD, Shapiro B, Bouffard A *et al.* Distinguishing benign from malignant euadrenal masses. *Ann Intern Med* 1988; **109**: 613–18.
19. Francis IR, Smid A, Gross MD, Shapiro B, Naylor B, Glazer GM. Adrenal masses in oncologic patients: functional and morphologic evaluation. *Radiology* 1988; **166**: 353–6.
20. Thompson NW, Cheung PSY. Diagnosis and treatment of functioning and nonfunctioning adrenocortical neoplasms including incidentalomas. *Surg Clin North Am* 1987; **67**: 423–36.

21. Egglin TK, Hahn PF, Stark DD. MRI of the adrenal glands. *Semin Roentgenol* 1988; **23**: 280–7.
22. Glazer GM, Woolsey EJ, Borrello J *et al*. Adrenal tissue characterization using MR imaging. *Radiology* 1986; **158**: 73–9.
23. Chezmar JL, Robbins SM, Nelson RC *et al*. Adrenal masses: characterization with T1-weighted MR imaging. *Radiology* 1988; **166**: 357–9.
24. Khafagi FA, Gross MD, Shapiro B, Glazer GM, Francis I, Thompson NW. Clinical significance of the large adrenal mass. *Br J Surg* 1991; **78**: 828–33.
25. Berkman WA, Bernardino M, Sewell CW, Barton Price R, Sones PJ. The computed tomography-guided adrenal biopsy: an alternative to surgery in adrenal mass diagnosis. *Cancer* 1984; **53**: 2098–103.
26. Heaston DK, Handel DB, Ashton PR, Korobin M. Narrow gauge needle aspiration of solid adrenal masses. *AJR Am J Roentgenol* 1982; **138**: 1143–8.
27. Bernardino ME, Walther MM, Phillips VM *et al*. CT-guided adrenal biopsy: accuracy, safety and indications. *AJR Am J Roentgenol* 1985; **144**: 67–9.
28. Kassirer JP. Our stubborn quest for diagnostic certainty: a cause of excessive testing. *N Engl J Med* 1989; **320**: 1489–91.
29. Herrera MF, Grant CS, Van Heerden JA, Sheedy PF, Ilstrup DM. Incidentally discovered adrenal tumors: an institutional perspective. *Surgery* 1991; **110**: 1014–21.
30. Bernardino ME. Management of the asymptomatic patient with a unilateral adrenal mass. *Radiology* 1988; **166**: 121–3.
31. O'Leary TJ, Ooi TC. The adrenal incidentaloma. *Can J Surg* 1986; **29**: 6–7.

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Announcement

British Association of Endocrine Surgeons

The British Association of Endocrine Surgeons has been pleased to be an affiliate society to *The British Journal of Surgery* and had the privilege of having abstracts refereed and, if suitable, published in the Journal.

The next meeting of the BAES will take place on 20–21 May 1993 in Bristol. If you wish to attend this meeting, details of registration and the programme can be obtained from Mrs P. Lee, Centre Manager, Edward Jenner Teaching Centre, Bristol Royal Infirmary, Bristol BS2 8HW. Telephone: 0272 282045. Facsimile: 0272 282052.

Details of membership can be obtained from the Secretary of the Society, Mr Tony Goode, at the following address: Mr A. Goode, Honorary Secretary, BAES, Academic Surgical Unit, The London Hospital, Whitechapel, London E1 1BB.

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Perioperative blood transfusion and outcome after resection for colorectal carcinoma

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The degree of immunomodulation by perioperative blood transfusion and its effect on oncological surgery remain controversial. A major problem with previous clinical studies has been the inadequate patient population in each and the presence of confounding variables. To resolve some of the controversy, all studies published between 1982 and 1990 were reviewed using the statistical method of Mantel–Haentszel–Peto to determine a cumulative estimate of the direction and magnitude of this association. Some 20 papers were included in the analysis, representing 5236 patients. The cumulative odds ratios (95 per cent confidence interval) of disease recurrence, death from cancer and death from any cause were 1·80 (1·30–2·51), 1·76 (1·15–2·66) and 1·63 (1·12–2·38) respectively. These results support the hypothesis that perioperative blood transfusion is associated with an increased risk of recurrence of colorectal carcinoma and death from this malignancy.

The degree of immunomodulation by perioperative blood transfusion and its resultant effect on oncological surgery remain controversial. A positive association between perioperative blood transfusion and recurrence of colorectal carcinoma was first reported by Burrows and Tartter[1] in 1982. Since that time numerous clinical studies, both supporting and disputing this association, have appeared in the literature. The strength, magnitude and mechanisms of this association are not clear from these studies. The retrospective nature of most makes it difficult to ascertain whether the association is one of cause and effect or merely an epiphenomenon.

The aim of the present work was to define the direction and magnitude of the association between blood transfusion and a negative outcome after resection of colorectal carcinoma, by combining the data from many different studies. The results from these were pooled and evaluated by the statistical methods of Mantel–Haentszel–Peto[2,3] to gain a cumulative estimate of the direction and magnitude of this association.

Statistical methods

Publications concerning the association of blood transfusion and outcome after resection for colorectal carcinoma appearing in the English language literature between 1982 and 1990 were retrieved by a computerized literature search (*MEDLINE*), a manual search of *Index Medicus* and by scanning the reference lists of identified studies. A total of 24 papers were identified[1,4–26]. Four studies[23–26] were excluded from further review because their results appeared in part or in whole in a previous publication.

The remaining 20 papers were reviewed independently by two of the authors (O.K.S., M.C.). The study design and period during which the study was undertaken were ascertained and the presence or absence of a number of criteria pertaining to study design were noted. A particular criterion was judged to be present only when both reviewers agreed; if not, the criterion was considered to be missing. Criteria examined included: definitions of inclusion and exclusion requirements; the patient population from which the study population was derived; type and duration of follow-up; definition of transfusion; and the type of outcome measures used. It was also noted whether survival curves were calculated from the data, whether a Cox regression analysis was performed to control for covariates, and what influence this analysis had on the study outcome. Covariates considered important for regression analysis were: age, sex, site of lesion (colon *versus* rectum), preoperative haematocrit, clinical stage (Dukes' classification) and blood transfusion. For the purpose of the present study a negative outcome was defined as death, death from cancer or recurrence of disease. For a study to be included in the present analysis it was required that the absolute number of negative outcomes in both transfused and non-transfused patients be available in the publication.

There was great variability among the studies with respect to the date and type of operation, type and location of neoplasm, and definition of perioperative blood transfusion. Statistical methods for combining results of different studies that assume homogeneity between them could therefore not be employed. The method of Mantel–Haentszel–Peto[2,3] does not make such an assumption because it does not compare subjects in one study with those in another. For this method it is assumed that studies addressing similar questions, with comparable outcome measures, should give results of the same qualitative direction, except for random error. For each study, the number of negative outcomes (death, cancer death or recurrence) within each group (transfused and not transfused) was summed. If transfusion is not associated with negative outcome after surgery and the number of patients in the transfused and non-transfused groups is equal, the difference in the number of negative outcomes between the two groups of patients should not differ significantly from zero.

For each study an observed minus expected ($O - E$) number of negative outcomes was calculated for the transfused group of patients. Details of these calculations and the calculation of the variance of the resulting statistic are described elsewhere[2,3]. Briefly, when a standard 2 × 2 table is constructed thus:

	Transfused	Non-transfused
Negative outcome	a	b
No negative outcome	c	d

then $O = a$, and $E = (a+b)(a+c)/N$, where $N = (a+b+c+d)$.

If transfusion is associated with negative outcome, $O - E > 0$ would be expected. $O - E$ and its variance can be

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used to test for statistical significance. The $O - E$ values from each study were summed to see whether the grand total (T_G) differed significantly from zero. If there was no association between transfusion and adverse outcome, $O - E$ should differ only randomly from zero and the sum of $O - E$ for all studies should approach zero as the number of studies included in the analysis approaches infinity. The grand total and its variance (V) can be used to test whether a significant association exists by the calculation of z, the number of standard deviations (s) that T_G differs from zero: $z = T_G/s$.

An odds ratio of negative outcomes for transfused *versus* non-transfused patients, along with the variance of this ratio, was calculated for each outcome measure from the data in each study. A cumulative odds ratio, summarizing the results of this series of heterogeneous studies, is estimated by $\exp(T_G/V)$ and the asymptotic 95 per cent confidence interval (c.i.) is given by $\exp(T_G/V \pm 1{\cdot}96/s)$. The percentage ($p$) by which this odds ratio differs from unity has a standard deviation of p/z. One outcome measure was selected from each study to calculate the cumulative odds ratio for all 17 studies (see below). If more than one outcome measure was given in any study, recurrence rate was selected above cancer death rate, which in turn was selected above death rate. Cumulative odds ratios were then calculated separately for recurrence rate, cancer death rate and death rate for the studies in which data were available.

Two-tailed P values were used in the analysis to determine statistical significance.

Statistical analysis

Twenty studies were included in the initial analysis, representing 5236 patients (*Table 1*). Surgery in the studies took place between 1951 and 1986, the majority of operations occurring in the late 1970s and early 1980s. Three publications concerned only patients with colonic carcinoma; the remaining 17 concerned colorectal carcinoma. The mean(s.d.) number of patients in each study was 262(147) and the mean(s.d.) proportion of patients receiving transfusion 66·3(12·0) per cent.

Eighteen papers detailed retrospective cohort studies and two prospective cohort studies[7,10] (*Table 2*). The population from which the study patients were derived was defined in 12 publications[6–15,19,22], inclusion criteria given in 18 cases[1,4–9,12–22], exclusion criteria in 17 papers[4–15,18–22], definition of transfusion in 15 cases[4,6–9,11–18,21,22], and type and/or duration of follow-up was defined in 17 (*Table 1*). In only seven studies were all five of these baseline criteria clearly defined.

Recurrence of carcinoma was used as an outcome in ten studies, death from cancer in eight and death in ten. A statistically significant association of a negative outcome with blood transfusion was reported in 11 publications[1,4,6,8,9,11,12,16–18,20]. In eight, no statistically significant association was

Table 2 *Odds ratio of a negative outcome in transfused* versus *non-transfused patients in 17 studies*

Reference	Outcome	Odds ratio (95% c.i.)
Weiden *et al.*[14]	Recurrence	0·63 (0·30–1·31)
Vente *et al.*[7]	Death	1·00 (0·54–1·85)
Frankish *et al.*[10]	Recurrence	1·02 (0·50–2·06)
Liewald *et al.*[17]	Recurrence	1·30 (0·74–2·26)
Ota *et al.*[5]	Cancer death	1·35 (0·62–2·94)
Francis *et al.*[13]	Recurrence	1·55 (0·60–4·00)
Jakobsen *et al.*[19]	Cancer death	1·61 (0·81–3·19)
Nathanson *et al.*[11]	Death	1·69 (1·12–2·56)
Ross[15]	Death	1·74 (0·91–3·33)
Parrott *et al.*[12]	Cancer death	2·03 (1·29–3·20)
Van Lawick Van Pabst *et al.*[18]	Cancer death	2·28 (0·82–6·38)
Voogt *et al.*[9]	Cancer death	2·36 (0·74–7·51)
Foster *et al.*[8]	Cancer death	2·41 (1·13–5·14)
Beynon *et al.*[16]	Recurrence	2·46 (1·59–3·79)
Wobbes *et al.*[4]	Recurrence	2·54 (1·41–4·57)
Burrows and Tartter[1]	Recurrence	5·13 (2·20–12·0)
Blumberg *et al.*[6]	Recurrence	7·67 (3·09–19·0)

c.i., Confidence interval

Table 1 *Baseline data from 20 studies*

Reference	Study period	Cancer type	No. of patients	No. transfused*	Follow-up
Weiden *et al.*[14]	1977–1979	Colorectal	171	103 (60·2)	5 years
Vente *et al.*[7]	1979–1982	Colorectal	212	158 (74·5)	5 years
Frankish *et al.*[10]	1981–1982	Colorectal	174	103 (59·2)	3 years
Liewald *et al.*[17]	1978–1985	Colorectal	439	304 (69·2)	Mean months
Ross[15]	1977–1980	Colorectal	159	95 (59·7)	5 years
Ota *et al.*[5]	1955–1975	Colonic	207	162 (78·3)	10 years
Nathanson *et al.*[11]	1972–1977	Colorectal	366	199 (54·4)	n.a.
Jakobsen *et al.*[19]	1978–1981	Colorectal	315	268 (85·1)	Median years
Francis *et al.*[13]	1974–1981	Colorectal	87	53 (61)	Mean months
Parrott *et al.*[12]	1974–1985	Colorectal	517	373 (72·1)	n.a.
Beynon *et al.*[16]	1969–1980	Colorectal	519	385 (74·2)	5 years
Wobbes *et al.*[4]	1975–1986	Colorectal	270	184 (68·1)	5 years
Van Lawick Van Pabst *et al.*[18]	1977–1985	Colorectal	164	117 (71·3)	Mean years
Voogt *et al.*[9]	1973–1978	Colonic	113	86 (76·1)	5 years
Foster *et al.*[8]	1974–1979	Colonic	146	65 (44·5)	Median months
Burrows and Tartter[1]	1976–1981	Colorectal	123	58 (47·2)	5 years
Blumberg *et al.*[6]	1970–1981	Colorectal	197	129 (65·5)	n.a.
Corman *et al.*[20]	1951–1971	Colorectal	400	347 (86·8)	10 years
Crowson *et al.*[21]	1981–1983	Colorectal	525	373 (71·0)	5 years
Marsh *et al.*[22]	1980–1984	Colorectal	132	62 (47·0)	Mean years
Total			5236	3624	
Median			207	158	
Mean(s.d.)			262(147)	(66·3(12·0))	

*Values in parentheses are percentages. n.a., Not available

Table 3 *Recorded postoperative negative outcomes in patients after resection for colorectal cancer in 17 studies*

		Negative outcomes		Statistical calculations		
Reference	Outcome	Transfused	Non-transfused	$O - E$	Variance	P*
Blumberg *et al.*[6]	Recurrence	56 of 129	6 of 68	15·4	13·5	<0·001
Burrows and Tartter[1]	Recurrence	28 of 58	10 of 65	10·1	10·3	<0·001
Wobbes *et al.*[4]	Cancer death	77 of 184	19 of 86	11·6	15·9	0·004
Beynon *et al.*[16]	Recurrence	179 of 385	35 of 134	20·3	27·4	<0·001
Foster *et al.*[8]	Cancer death	23 of 65	15 of 81	6·08	9·59	0·05
Voogt *et al.*[9]	Cancer death	25 of 86	4 of 27	2·93	4·5	n.s.
Van Lawick Van Pabst *et al.*[18]	Cancer death	25 of 117	51 of 47	3·6	5·96	n.s.
Parrott *et al.*[12]	Cancer death	130 of 373	30 of 144	14·6	25·2	0·004
Ross[15]	Death	63 of 95	34 of 64	5·04	9·89	n.s.
Nathanson *et al.*[11]	Death	113 of 199	73 of 167	11·9	25·6	0·02
Jakobsen *et al.*[19]	Cancer death	102 of 268	13 of 47	4·66	9·75	n.s.
Francis *et al.*[13]	Recurrence	19 of 53	9 of 34	1·94	5·08	n.s.
Ota *et al.*[5]	Cancer death	45 of 162	10 of 45	1·96	7·3	n.s.
Liewald *et al.*[17]	Recurrence	56 of 304	20 of 135	3·37	14·4	n.s.
Frankish *et al.*[10]	Recurrence	25 of 103	17 of 71	0·14	7·82	n.s.
Vente *et al.*[7]	Death	76 of 158	26 of 54	0	10·3	n.s.
Weiden *et al.*[14]	Recurrence	19 of 103	18 of 68	−3·3	5·99	n.s.
Total				110	209	<0·001

$O - E$, observed minus expected; n.s., not significant; *two-tailed table of z. Cumulative odds ratio 1·69 (95 per cent confidence interval 1·31–2·19); typical odds increase(s.d.) of negative outcome after perioperative transfusion 69(9·1) per cent

found[5,7,10,13–15,19,21]. In the remaining study, a significant association was seen with the transfusion of whole blood and plasma, but none when 'any transfusion' was used as the variable[22].

In 12 papers[4,6,8,9,11,14,17–22] an attempt was made to control for covariates by performing Cox multiple regression analysis. In ten cases, regression analysis did not alter the initial conclusion. In one study, which initially demonstrated a significant association, Cox analysis showed an association of blood transfusion with death, but not with recurrence of carcinoma[17]. In another, an association was found when the number of units transfused was used as the variable, but not when presence or absence of blood transfusion was employed[20]. Other variables associated with adverse outcome by Cox regression in more than one study included: Dukes' class[4,8,9,11,18–21], location of the primary neoplasm in the rectum[6,8–11,19,20], histological grade[4,8] and age of the patient[6,21]. Variables found to be significantly associated with transfusion by more than one author were: lesion located in the rectum[4,6,8,10–13,17–20] or right colon[6,13], preoperative haemoglobin level[4,6,8,9,12,13,15,19–21], duration of surgery[6,12,19], operative blood loss[12,18] and age[6,8].

Data were available for further analysis in 17 studies. *Table 3* shows the results of each of these in terms of the number of patients suffering a negative outcome in transfused and non-transfused groups. In 15 of the 17 studies, an adverse outcome was seen more commonly in the transfused group of patients (*Tables 3* and *4*). The number of patients suffering a negative outcome in the transfused group was significantly higher in six cases ($O - E > 0$, $P < 0·05$). In one study[7] a negative outcome was equally common in the transfused and the non-transfused groups. In one study[14] a negative outcome was more common in the non-transfused group ($O - E < 0$). The grand total of all 17 $O - E$ values in *Table 3* was 110 (the variance of T_G was 209 and s.d. 14·46; T_G is 7·6 s.d. from zero, thus $P < 0·001$ two-tailed), indicating that a negative outcome was significantly more frequent in transfused patients.

For the 17 studies used in the analysis, the overall odds ratio of suffering a negative outcome in the transfused *versus* non-transfused group was 1·69 (95 per cent c.i. 1·31–2·19) (*Table 3; Figure 1*). This represents an increase in the odds(s.d.) of suffering an adverse outcome in the transfused group of 69(9·1) per cent. The overall odds ratios (95 per cent c.i.) were calculated separately for recurrence as 1·80 (1·30–2·51), death from cancer as 1·76 (1·15–2·66) and death as 1·63 (1·12–2·38) (*Table 4; Figure 2*).

Discussion

Over the past 20 years, the effect of blood transfusion on the immune system has been studied and shown to cause suppression. This immunosuppression is felt to be beneficial in organ transplantation[27] and in disorders such as inflammatory bowel disease[28], but is hypothesized to be detrimental in oncological surgery where immune surveillance is important in detecting and eliminating circulating malignant cells. The first study linking recurrence of colorectal carcinoma with perioperative blood transfusion was reported by Burrows and Tartter[1] in 1982. Since that time there have been numerous clinical studies both supporting and disputing this association. In addition, a relationship between perioperative blood transfusion and decreased survival and/or recurrence of malignancy has been reported after surgery for breast[29], lung[30,31], renal cell[32] and cervical[33] carcinomas, head and neck neoplasms[34] and sarcomas[35].

The present results indicate an association between perioperative blood transfusion and negative outcome as measured by recurrence of disease, cancer death and death. The estimated cumulative odds ratio of a negative outcome in the presence of transfusion is 1·69. This represents a point estimate of an increase in the odds of suffering a negative outcome for transfused patients of 69 per cent. The calculated odds ratio of disease recurrence, cancer death and death in transfused patients are 1·80, 1·76 and 1·63 respectively.

The advantage of combining results from a number of studies is the larger sample size. In this analysis, the sample used to calculate the overall odds ratio of negative outcome among transfused patients is greater than 5000 patients. Overall outcomes calculated from such a large sample are less prone to random error than the results of individual studies. When several studies are carried out to investigate the same

Table 4 *Odds ratio of a negative outcome after perioperative blood transfusion*

	Negative outcome		Statistical calculations		
Reference	Transfused	Non-transfused	*O* − *E*	Variance	*P**
Recorded episodes of cancer recurrence after resection for colorectal cancer†					
Blumberg *et al.*[6]	56 of 129	6 of 68	15·4	13·5	<0·001
Wobbes *et al.*[4]	77 of 184	19 of 86	11·6	15·9	0·004
Beynon *et al.*[16]	179 of 385	35 of 134	20·3	27·4	<0·003
Francis *et al.*[13]	19 of 53	9 of 34	1·96	5·08	n.s.
Liewald *et al.*[17]	56 of 304	20 of 135	3·37	14·4	n.s.
Frankish *et al.*[10]	25 of 103	17 of 71	0·14	7·82	n.s.
Weiden *et al.*[14]	14 of 103	18 of 68	−3·3	5·99	n.s.
Total			49·75	90·09	<0·001
Recorded cancer deaths in patients after resection for colorectal cancer‡					
Blumberg *et al.*[6]	22 of 129	3 of 68	5·63	6·67	0·031
Foster *et al.*[8]	23 of 65	15 of 81	6·08	9·59	0·05
Voogt *et al.*[9]	25 of 86	4 of 27	2·93	4·50	n.s.
Van Lawick Van Pabst *et al.*[18]	25 of 117	5 of 47	3·60	5·96	n.s.
Parrott *et al.*[12]	130 of 373	30 of 144	14·6	25·2	0·004
Jakobsen *et al.*[19]	102 of 268	13 of 47	4·16	9·75	n.s.
Ota *et al.*[5]	45 of 162	10 of 45	1·96	7·3	n.s.
Total			38·96	69·06	<0·001
Recorded death in patients after resection for colorectal cancer§					
Wobbes *et al.*[4]	79 of 184	24 of 86	8·81	15·7	0·026
Foster *et al.*[8]	33 of 65	30 of 81	4·95	10·6	n.s.
Voogt *et al.*[9]	45 of 86	7 of 27	5·42	5·88	0·025
Van Lawick Van Pabst *et al.*[18]	39 of 117	8 of 47	5·47	8·12	n.s.
Parrott *et al.*[12]	177 of 373	49 of 144	13·9	27·9	0·009
Ross[15]	63 of 95	34 of 64	5·04	9·89	n.s.
Nathanson *et al.*[11]	113 of 199	73 of 167	11·9	25·6	0·019
Vente *et al.*[7]	76 of 158	26 of 54	0·0	10·3	n.s.
Total			55·49	113·99	<0·05

O − *E*, observed minus expected; n.s., not significant; *two-tailed table of *z*. Cumulative odds ratio (95 per cent confidence interval): †1·80 (1·30–2·51); ‡1·76 (1·15–2·66); §1·63 (1·12–2·38). Odds increase(s.d.) of negative result after perioperative transfusion: †80(15·4) per cent; ‡76(16·2) per cent; §63(12·1) per cent

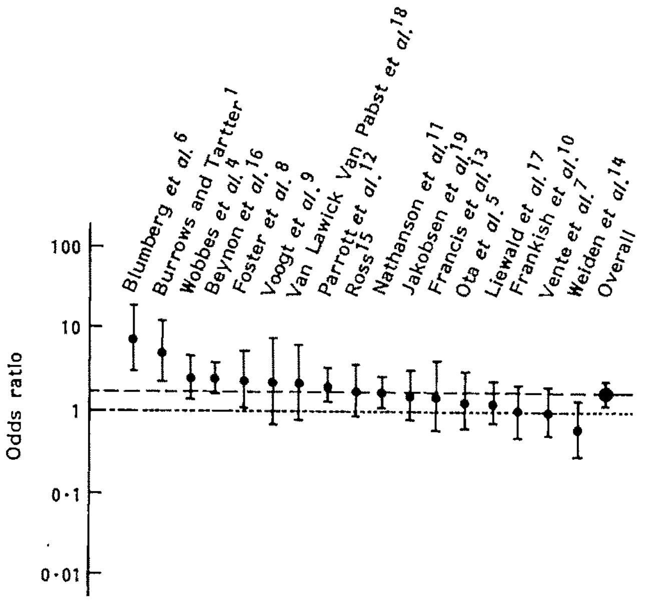

Figure 1 *Odds ratios (95 per cent confidence interval) of a negative outcome after perioperative blood transfusion. ---, Cumulative odds ratio; -----, odds ratio of no increased risk*

phenomenon the results of some may become better known than others. By combining the results from all known studies in the literature to date, regardless of the direction or magnitude of their outcomes, an attempt has been made to obtain an overall estimate of the association of blood transfusion with negative outcome after surgery for colorectal carcinoma.

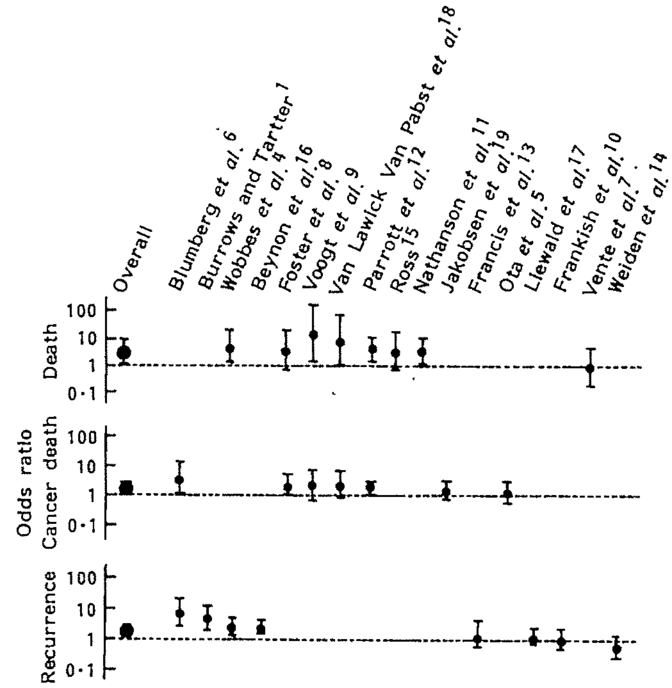

Figure 2 *Odds ratios (95 per cent confidence interval) of recurrence, cancer death and death after perioperative blood transfusion. Gaps indicate studies giving insufficient information to allow calculation of the odds ratio. -----, Odds ratio of no increased risk*

In the present instance, the method of Mantel–Haentszel–Peto[2,3] was attractive, as it was not necessary to assume that the association of transfusion between studies was of the same magnitude, nor that the measured outcomes were equivalent between studies. The assumptions necessary for this method[2,3] are: first, no bias occurs in the selection of studies to be included in the analysis; and second, within each study the comparison of outcome between transfused and non-transfused patients is not subject to substantial bias. The first assumption has been satisfied, since all published studies were included from which sufficient data were available for the calculations. However, it is conceivable that studies in which a positive association between transfusion and negative outcome was found were more likely to be published than those in which no such association was found. No attempt was made to include unpublished data in this analysis to evaluate the effect of such publication bias. It is recognized that the second assumption is more difficult to satisfy in non-randomized prospective and retrospective studies; it represents a weakness in this type of assessment.

When performing a retrospective study it is difficult to control for sources of bias. It is, therefore, important that the study design is clearly portrayed by including definitions of the interventions, inclusion and exclusion criteria, study population, and outcome measures in the publication. These definitions, when clearly stated, will help in the interpretation of results. Unfortunately, only six of the 17 publications used in the analysis included clear definitions of all the above design criteria. In 12 studies, Cox multiple regression analysis was performed to control for covariates. Initial findings were altered in only one of these after regression analysis.

The present analysis demonstrates a significant association between perioperative blood transfusion and negative outcome. Because of the retrospective nature of most of the studies and the quality of the data, it is not possible to say whether transfusion is responsible for the worse outcome among transfused patients or whether it is due to one or more confounding variables. For example, in almost all studies included in the analysis, patients with rectal carcinoma were more likely to be transfused than those with colonic tumours. Cox regression analysis in a number of studies[4,6,8,10–13,17–20] revealed that rectal carcinoma was independently associated with blood transfusion. Since it has been shown that rectal cancer has a higher recurrence rate than carcinoma of the colon[36,37], it may be that transfusion is a marker for poor prognostic factors, such as position of the primary neoplasm in the rectum. The data were not available in the publications to allow separate analysis when stratified with respect to such potential confounders as site of lesion, histological grade, stage of disease, presence of concomitant illness, haematocrit at presentation and age of patient.

The mechanisms by which blood transfusion may cause immunosuppression concern cell-mediated immunity and macrophage migration[38]. Studies have shown that traumatized animals that are transfused have decreased cell-mediated immunity[39], and that haemorrhage and transfusion without tissue trauma results not only in decreased cell-mediated immunity, as measured by the mixed lymphocyte reaction, but also increased susceptibility to sepsis[40]. The results of animal experiments are supported by human studies, which show that patients who receive multiple blood transfusions have a reversal of the T4/T8 ratio; the proportion of T helper lymphocytes is decreased in relation to T suppressor cells[41,42]. This effect may last for up to 8 months after transfusion[43]. In addition, natural killer activity in these patients is decreased[44]. The link between transfusion, cell-mediated immunity and malignancy has been reported in two murine models. In one study, both immunocompetent transfused mice and athymic mice had increased melanoma growth compared with immunocompetent and non-transfused controls[45]. In another, mice with neuroblastomas that received allogeneic blood transfusion had decreased cell-mediated immunity and increased tumour growth[46].

The mechanisms by which blood transfusion causes these abnormalities are unknown. The impairment in cell-mediated immunity may result from decreased interleukin (IL) 2 production or abnormal macrophage migration[47]. IL-2 is necessary for the activation of B lymphocytes and regulation of T lymphocyte production, and macrophage migration is regulated in part by the powerful immunosuppressant prostaglandin (PG) E_2. It has been shown that PGE_2 levels rise after blood transfusion[48]. Furthermore, decreased macrophage migration and antigen presentation, as measured by lymphocyte blastogenesis, have been shown after transfusion[49]. Although the non-specific immunomodulation by blood transfusion probably relates to its effect on PGE_2 and IL-2, other mediators, such as serum factors and metabolites of the arachidonic acid pathway, may be involved[38].

Immunomodulation by transfusion may be due in part to the associated iron load[50]. This theory has been supported by both *in vitro* and *in vivo* studies. It has been shown *in vitro* that increased serum iron leads to decreased lymphocytic response to antigens[51]. *In vivo* studies in patients with thalassaemia link decreased mitogen response with increasing ferritin levels[52]. Furthermore, phagocytosis of damaged transfused erythrocytes has been shown to result in decreased lymphocyte function and may in part explain decreased renal allograft rejection in patients receiving blood transfusion[53].

Because transfusion-related immunomodulation is thought to be non-specific, there should be an increased rate of infectious complications associated with blood transfusion. In one animal report[54] and two retrospective clinical studies (one involving colorectal[55], the other gastric[56] surgery) an association between blood transfusion and perioperative infectious complications has been demonstrated.

Evidence that allogeneic blood transfusion results in immune suppression is increasing. Although this effect may be beneficial in transplantation and certain diseases where immunosuppression is advantageous, it may be detrimental in cancer surgery. The results of this study support the hypothesis that perioperative blood transfusion is associated with subsequent increased risk of recurrence of colorectal carcinoma and death from this malignancy. However, because of the retrospective nature of most of the data, it is not possible to say that transfusion is responsible for this increased negative outcome. It has been suggested that 25–28 per cent of patients undergoing resection for colorectal carcinoma receive at least 1 unit unnecessary blood[57]. The risks of transfusion-transmitted infection and transfusion reaction are well recognized; they alone provide ample reason for careful justification for each transfused unit of blood. The possible risk of increased tumour recurrence and death from colorectal carcinoma due to transfusion-mediated immunomodulation may also need to be considered.

References

1. Burrows L, Tartter P. Effect of blood transfusion on colonic malignancy recurrence rate. *Lancet* 1982; **ii**: 662 (Letter).
2. Antiplatelet Trialists' Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. *BMJ* 1988; **296**: 320–31.
3. Yusef S, Peto R, Lewis J *et al.* Beta blockade during and after myocardial infarction: an overview of randomized trials. *Prog Cardiovasc Dis* 1985; **27**: 335–71.
4. Wobbes T, Joosen KHG, Kuypers HHC *et al.* The effect of packed cells and whole blood transfusions on survival after curative resection for colorectal carcinoma. *Dis Colon Rectum* 1989; **32**: 743–8.
5. Ota D, Alvarez L, Lichtiger B *et al.* Perioperative blood transfusion in patients with colon carcinoma. *Transfusion* 1985; **25**: 392–4.
6. Blumberg N, Agarwal MM, Chuang C. Relation between recurrence of cancer of the colon and blood transfusion. *BMJ* 1985; **290**: 1037–9.
7. Vente JP, Wiggers Th, Weidema WF *et al.* Peri-operative blood transfusions in colorectal cancer. *Eur J Surg Oncol* 1989; **15**: 371–4.
8. Foster RS, Costanza MC, Foster JC *et al.* Adverse relationship between blood transfusions and survival after colectomy for colon cancer. *Cancer* 1985; **55**: 1196–201.
9. Voogt PJ, van der Velde CJ, Brand A *et al.* Perioperative blood

transfusion and cancer prognosis. *Cancer* 1987; **59**: 836–43.

10. Frankish PD, McNee RK, Alley PG *et al.* Relationship between cancer of the colon and blood transfusion. *BMJ* 1985; **290**: 1827 (Letter).
11. Nathanson SD, Tilley BC, Schultz L *et al.* Perioperative allogenic blood transfusions: survival in patients with resected carcinomas of the colon and rectum. *Arch Surg* 1985; **120**: 734–8.
12. Parrott NR, Lennard TWJ, Taylor RMR *et al.* Effect of perioperative blood transfusion on recurrence of colorectal cancer. *Br J Surg* 1986; **73**: 970–3.
13. Francis DMA, Judson RT. Blood transfusion and the recurrence of cancer of the colon and rectum. *Br J Surg* 1987; **74**: 26–30.
14. Weiden PL, Bean MA, Schultz P. Perioperative blood transfusion does not increase the risk of colorectal cancer recurrence. *Cancer* 1987; **60**: 870–4.
15. Ross WB. Blood transfusion and colorectal cancer. *J R Coll Surg Edinb* 1987; **32**: 197–201.
16. Beynon J, Davies PW, Billings PJ *et al.* Perioperative blood transfusion increases the risk of recurrence in colorectal cancer. *Dis Colon Rectum* 1989; **32**: 975–9.
17. Liewald F, Wirsching RP, Zulke C *et al.* Influence of blood transfusions on tumor recurrence and survival rate in colorectal carcinoma. *Eur J Cancer* 1990; **26**: 327–35.
18. Van Lawick Van Pabst WP, Langenhorst BL, Mulder PGH *et al.* Effect of perioperative blood loss and perioperative blood transfusions on colorectal cancer survival. *Eur J Cancer Clin Oncol* 1988; **24**: 741–7.
19. Jakobsen EB, Eickhoff JH, Andersen J *et al.* Perioperative blood transfusion and recurrence and death after resection for cancer of the colon and rectum. *Scand J Gastroenterol* 1990; **25**: 435–42.
20. Corman J, Arnoux R, Peloquin A *et al.* Blood transfusions and survival after colectomy for colorectal cancer. *Can J Surg* 1986; **29**: 325–9.
21. Crowson MC, Hallissey MT, Kiff RS *et al.* Blood transfusion in colorectal cancer. *Br J Surg* 1989; **76**: 522–3.
22. Marsh J, Donnan PT, Hamer-Hodges DW. Association between transfusion with plasma and the recurrence of colorectal carcinoma. *Br J Surg* 1990; **77**: 623–6.
23. Corman J, Arnoux R, Peloquin A *et al.* Perioperative blood transfusions and colorectal cancer outcome. *Transplant Proc* 1988; **20**: 1128–9.
24. Arnoux R, Corman J, Peloquin A *et al.* Adverse effect of blood transfusions on patient survival after resection of rectal cancer. *Can J Surg* 1988; **31**: 121–6.
25. Parrott NR, Taylor RMR, Lennard TWJ *et al.* The blood transfusion effect and colorectal cancer recurrence. *Transplant Proc* 1987; **19**: 1475.
26. Foster RS, Costanza M, Foster JC *et al.* Blood transfusions and survival after resection of cancers of the breast, colon, and lung: the need for prospective randomized trials. *Transplant Proc* 1988; **20**: 1125–7.
27. Opelz G, Terasaki PI. Improvement of kidney-graft survival with increased numbers of transfusions. *N Engl J Med* 1978; **299**: 799–803.
28. Fry RD, Fleshman JW, Kodner IJ. Effect of perioperative blood transfusion on recurrence of Crohn's disease. *Lancet* 1989; **ii**: 1048 (Letter).
29. Tartter PI, Burrows L, Papatestas AE *et al.* Perioperative blood transfusion has prognostic significance for breast cancer. *Surgery* 1985; **97**: 225–30.
30. Hyman NH, Foster RS, DeMeules JE *et al.* Blood transfusion and survival after lung cancer resection. *Am J Surg* 1985; **149**: 502–7.
31. Little AG, Huai-shen W, Ferguson MK *et al.* Perioperative blood transfusion adversely affects prognosis in patients with stage I non-small cell lung cancer. *Am J Surg* 1990; **160**: 630–3.
32. Moffat LEF, Sunderland GT. Relation between recurrence of cancer and blood transfusion. *BMJ* 1985; **291**: 971.
33. Blumberg N, Agarwal M, Chuang C. A possible association between survival time and transfusion in patients with cervical cancer. *Blood* 1985; **66**(Suppl 1): 274.
34. Johnson JT, Taylor FH, Thearle PB. Blood transfusion and outcome in stage III head and neck carcinoma. *Arch Otolaryngol Head Neck Surg* 1987; **113**: 307–10.
35. Rosenberg SA, Seipp CA, White DE *et al.* Perioperative blood transfusions are associated with increased rates of recurrence and decreased survival in patients with high grade soft-tissue sarcomas of the extremities. *J Clin Oncol* 1985; **3**: 693–709.
36. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal carcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986; **ii**: 996–9.
37. Heald RJ, Ryall RDH. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986; **i**: 479–80.
38. Brunson ME, Alexander JW. Mechanisms of transfusion-induced immunosuppression. *Transfusion* 1990; **30**: 651–8.
39. Waymack JP, Rapien J, Garnett D, Tweddell JS *et al.* Effect of transfusion on immune function in a traumatized animal model. *Arch Surg* 1986; **121**: 50–4.
40. Stephan RN, Kupper TS, Geha AS *et al.* Hemorrhage without tissue trauma produces immunosuppression and enhances susceptibility to sepsis. *Arch Surg* 1987; **122**: 62–8.
41. Kaplan J, Sanaik S, Gitlin J, Lusher J. Diminished helper/suppressor lymphocyte ratios and natural killer activity in recipients of repeated blood transfusions. *Blood* 1984; **64**: 308–10.
42. Luban NLC, Kelleher JF, Zaloudek J, Reaman GH. Chronic transfusion alters T lymphocyte subpopulations in children with sickle cell disease. *Blood* 1984; **62**: 114A.
43. Tartter PI, Heimann TM, Aufsus AH. Blood transfusion, skin test reactivity, and lymphocytes in inflammatory bowel disease. *Am J Surg* 1986; **151**: 358–61.
44. Gascon P, Zoumbos NC, Young NS. Immunologic abnormalities in patients receiving multiple blood transfusions. *Ann Intern Med* 1984; **100**: 173–7.
45. Francis DMA, Burren CP, Clunie GJA. Acceleration of B16 melanoma growth in mice after blood transfusion. *Surgery* 1987; **102**: 485–92.
46. Lieberman MD, Shou J, Sigal RK *et al.* Transfusion-induced immunosuppression results in diminished host survival in a murine neuroblastoma model. *J Surg Res* 1990; **48**: 498–503.
47. Wood ML, Gottschalk R, Monaco AP. Effect of blood transfusion on IL-2 production. *Transplantation* 1988; **45**: 930–5.
48. Waymack JP, Gallon L, Barcelli U *et al.* Effect of blood transfusion on immune function. III. Alterations in macrophage arachidonic acid metabolism. *Arch Surg* 1987; **122**: 56–60.
49. Waymack JP, McNeal N, Warden GD *et al.* Effect of blood transfusions on macrophage–lymphocyte interaction in an animal model. *Ann Surg* 1986; **204**: 681–5.
50. DeSouza SA. Blood transfusion and allograft survival: iron related immunosuppression? *Lancet* 1983; **ii**: 681–2.
51. Matzner Y, Hershko C, Polliack A *et al.* Suppressive effect of ferritin on *in vitro* lymphocyte function. *Br J Haematol* 1979; **42**: 345–53.
52. Munn CG, Markson AL, Kapadia A, DeSouza M. Impaired T-cell mitogen response in some patients with thalassemia intermedia. *Thymus* 1981; **3**: 119–28.
53. Keown PA, Descamps B. Improved renal allograft survival after blood transfusion: a non-specific, erythrocyte-mediated immunoregulatory process? *Lancet* 1979; **i**: 20–2.
54. Waymack JP, Warden JD, Alexander JW *et al.* Effect of blood transfusion and anesthesia on resistance to bacterial peritonitis. *J Surg Res* 1987; **42**: 528–35.
55. Tartter PI, Quintero S, Barron DM. Perioperative blood transfusion associated with infectious complications after colorectal cancer operations. *Am J Surg* 1986; **152**: 479–82.
56. Pinto V, Baldonedo R, Nicolas C *et al.* Relationship of transfusion and infectious complications after gastric carcinoma operations. *Transfusion* 1991; **31**: 114–8.
57. Tartter PI, Barron DM. Unnecessary blood transfusions in elective colorectal cancer surgery. *Transfusion* 1985; **25**: 113–15.

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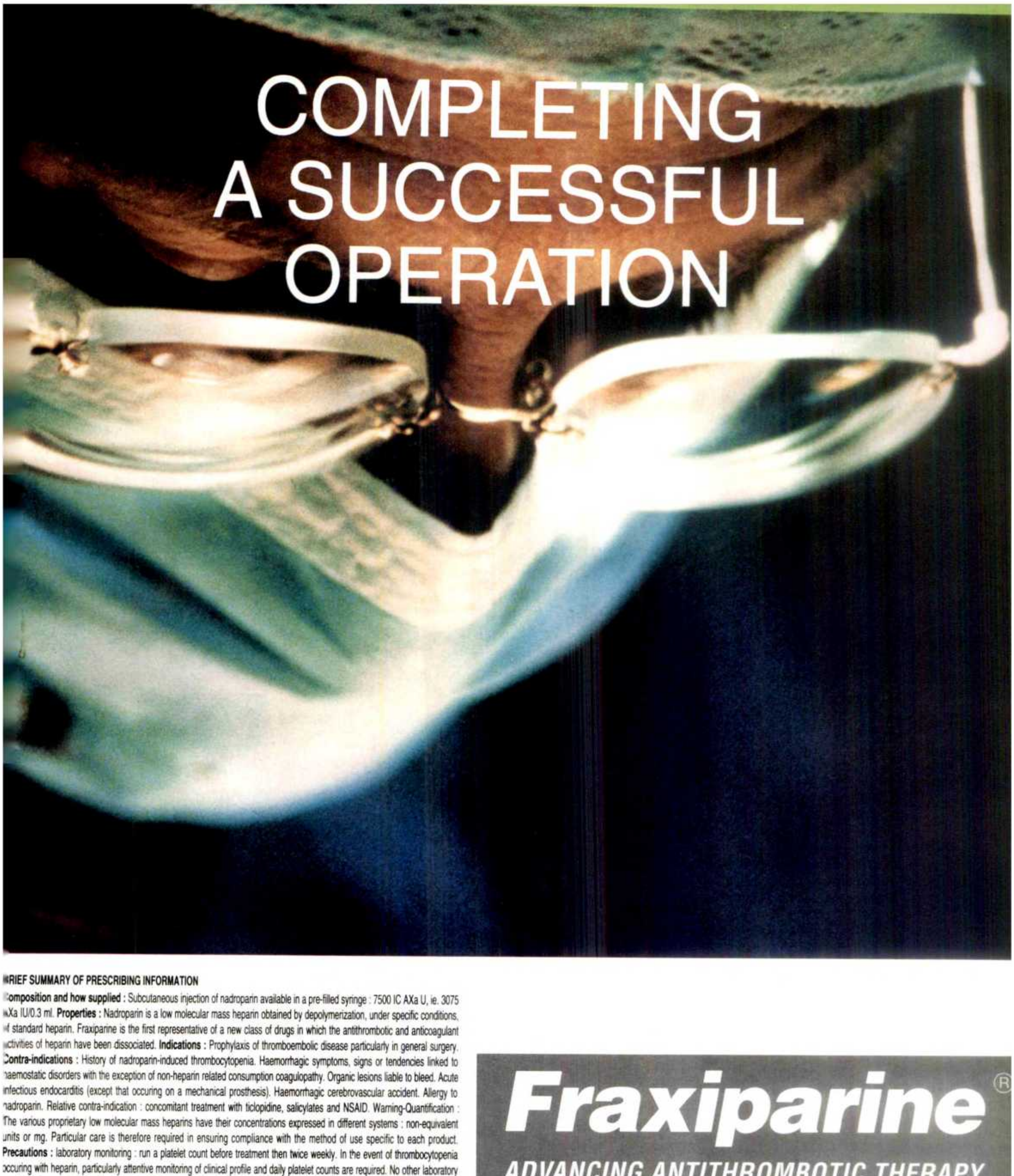

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Composition and how supplied : Subcutaneous injection of nadroparin available in a pre-filled syringe : 7500 IC AXa U, ie. 3075 aXa IU/0.3 ml. **Properties :** Nadroparin is a low molecular mass heparin obtained by depolymerization, under specific conditions, of standard heparin. Fraxiparine is the first representative of a new class of drugs in which the antithrombotic and anticoagulant activities of heparin have been dissociated. **Indications :** Prophylaxis of thromboembolic disease particularly in general surgery. **Contra-indications :** History of nadroparin-induced thrombocytopenia. Haemorrhagic symptoms, signs or tendencies linked to haemostatic disorders with the exception of non-heparin related consumption coagulopathy. Organic lesions liable to bleed. Acute infectious endocarditis (except that occuring on a mechanical prosthesis). Haemorrhagic cerebrovascular accident. Allergy to nadroparin. Relative contra-indication : concomitant treatment with ticlopidine, salicylates and NSAID. Warning-Quantification : The various proprietary low molecular mass heparins have their concentrations expressed in different systems : non-equivalent units or mg. Particular care is therefore required in ensuring compliance with the method of use specific to each product. **Precautions :** laboratory monitoring : run a platelet count before treatment then twice weekly. In the event of thrombocytopenia occuring with heparin, particularly attentive monitoring of clinical profile and daily platelet counts are required. No other laboratory monitoring is required. Caution is required in the event of liver failure, kidney failure, hypertension, history of gastro-intestinal ulcer or any other organic lesion liable to bleed. Caution is also required in cases of vascular disease of the chorioretina and in post-operative period after brain or spine surgery. As a precaution and in the absence of clinical experience, nadroparin should not be advised during pregnancy and lactation. **Drug interactions :** Due to an increased risk of haemorrhage : inadvisable combinations : acetylsalicylic acid, other salycilates (systemic route), NSAID (systemic route) and ticlodipine. Combinations requiring precautions (clinical and biological monitoring) : oral anticoagulants, glucocorticoids (systemic route), dextran 40 (parenteral route). **Adverse effects :** Haemorrhagic manifestations. A few rare cases of thrombocytopenia, sometimes serious have been reported. A few rare cases of cutaneous necrosis mainly occuring at the injection site have been reported with the heparins and low molecular mass heparins. These phenomena are preceded by purpura or erythematous plaque infiltrated and painful, with or without general signs. Treatment must immediately be suspended. Exceptionally, small haematomas are observed at the injection site. Cutaneous or systemic allergic manifestations are rare. In certain cases, development of such reactions necessitates treatment discontinuation. Elevated transaminases. **Use and dosage :** Fraxiparine is administered subcutaneously. Prophylactic treatment of thromboembolic disease in general surgery : effective prevention is based on a single daily injection of 0.3 ml Fraxiparine. The first injection is given 2 to 4 hours before surgery and the general duration of the treatment is at least 7 days. In all cases, prophylaxis needs to be pursued throughout the risk period and at least until the patient resumes active ambulation. Laboratory monitoring is not necessary. Overdosage : Protamine sulphate or hydrochloride administered by slow intravenous injection/ For more detailed information, consult your Sanofi Winthrop representative or see prescribing information. Sanofi Winthrop - Medical and scientific information Department - 94258 Gentilly Cedex France.

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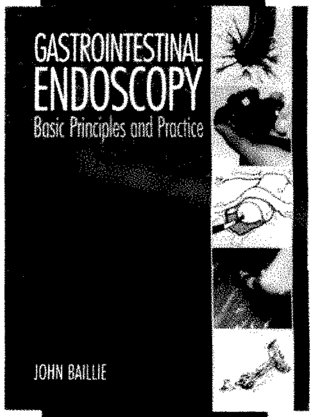

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Br. J. Surg. 1993, Vol. 80, April, 433–435

Hyperaemic response in the skin microcirculation of patients with chronic venous insufficiency

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The capacity of the microcirculation in the liposclerotic skin of patients with chronic venous insufficiency to vasodilate in response to pilocarpine electrophoresis was assessed using laser Doppler fluxmetry. Pilocarpine induces vasodilatation by direct action on capillaries; other methods of vasodilatation, such as heating of the skin, act by a number of pathways including a neurogenic one. Thirty patients with lipodermatosclerosis and chronic venous insufficiency and 20 control subjects were studied. There was no difference in peak vasodilatation following pilocarpine electrophoresis in the two groups. The median (interquartile range) peak flux in patients was 665 (382–1025) units and in controls 765 (452–975) units (95 per cent confidence interval of difference −270 to 150 units, P = 0·5). This suggests that the capillaries in the liposclerotic skin of patients with chronic venous insufficiency have a normal capacity to vasodilate.

Recent studies have reported a reduced hyperaemic response of the liposclerotic skin in patients with chronic venous insufficiency following ischaemia or heating[1–4]. The capacity of the microcirculation to support an increased blood flow is important for tissue repair after injury and is relevant to research into the pathogenesis of skin damage and ulceration in chronic venous insufficiency. Many of the data supporting the hypoxic basis for such damage come from studies showing reduced transcutaneous oxygen tension in liposclerotic skin[5–8]. Since the technique of transcutaneous oximetry relies on a normal capacity of the skin microcirculation to vasodilate in response to heating to 43–44°C, impairment of vasodilatation would invalidate any results obtained by this method. Stimuli such as heating and cuff ischaemia result in vasodilatation of skin capillaries through a number of mechanisms including increased local metabolism, alteration in sympathetic nervous outflow, and the axon flare reflex. Impairment of vasodilatation does not necessarily denote an abnormality of capillary function; it may indicate failure of the pathways by which the stimulus affects the capillaries.

The aim of this study was to determine whether the vasodilatory capacity of liposclerotic skin of patients with chronic venous insufficiency was impaired when using a direct method of stimulating capillaries. Pilocarpine causes vasodilatation by stimulating the muscarinic acetylcholine receptors in the vascular endothelium, provoking it to release endothelium-derived relaxing factor, a potent vasodilator[9]. This direct method of vasodilatation avoids the influence of factors such as neural control of the microcirculation that may themselves be affected by venous hypertension. It can be regarded as a measure of capillary responsiveness *per se*, rather than reflecting the total vasodilatory capacity of the skin microcirculation.

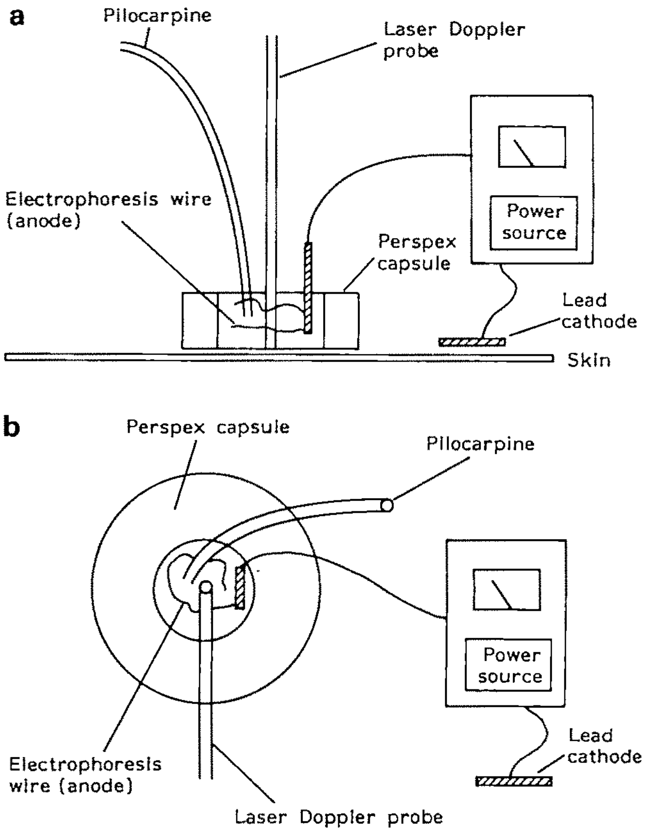

Figure 1 *Capsule used for pilocarpine electrophoresis.* **a** *Side view;* **b** *top view*

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Patients and methods

A total of 50 non-diabetic subjects with ankle:brachial pressure indices >0·9 were studied. Twenty men and ten women of median age 69 (interquartile range 52–73) years, with lipodermatosclerosis without ulceration and chronic venous insufficiency comprised the group with disease. In all cases the presence of significant venous valvular incompetence was demonstrated in the deep or superficial veins using duplex scanning (Acuson, Mountain View, California, USA) by an experienced operator. Twenty normal subjects, eight men and 12 women of median age 60 (interquartile range 49–69) years with no history or clinical evidence of venous disease, comprised the control group. Microcirculatory measurements were made in an environmental chamber with an ambient temperature of 22°C and a relative humidity of 30 per cent. The subjects were studied in the supine position and the investigation began after an acclimatization period of 20 min.

Pilocarpine electrophoresis was performed using the technique described by Parkhouse and Le Quesne[10]. A perspex capsule was attached 5 cm proximal to the medial malleolus in controls and on a nearby area of deep pigmentation in patients with lipodermatosclerosis, using double-sided adhesive tape. This capsule contained a chamber 5 mm in diameter into which pilocarpine was placed. The chamber also contained a platinum wire that acted as the anode for electrophoresis. A laser Doppler probe (PF109; Perimed, Stockholm, Sweden) was passed through a central hole in the roof of the chamber so that the tip was in contact with the skin (*Figures 1a* and *1b*). A solution of 1 per cent pilocarpine was placed in the chamber within the capsule. Once a stable basal flux was obtained from the laser Doppler fluxmeter (PF2; Perimed), pilocarpine electrophoresis was started by passing a 1-mA current between the platinum wire in the chamber and a lead plate placed on the calf of the patient. This resulted in electrophoresis of the pilocarpine into the skin and vasodilatation, usually within 5 min, which reached a peak within 5–10 min. No attempt was made to analyse the time taken to peak flux since this is dependent on the time taken for electrophoresis of pilocarpine to occur which is, in turn, dependent on skin quality.

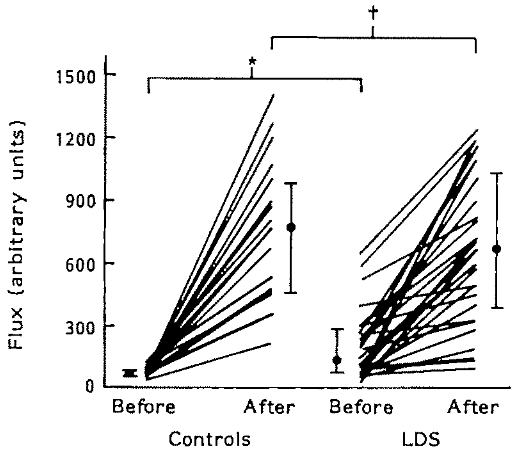

Figure 2 *Laser Doppler flux before and after pilocarpine electrophoresis in the gaiter area of controls and patients with lipodermatosclerosis (LDS). Bars are median (interquartile range).* *P = *0·004;* †P *not significant (Mann–Whitney* U *test)*

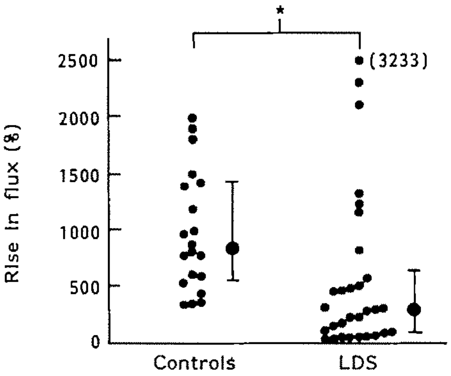

Figure 3 *Percentage rise in laser Doppler flux after pilocarpine electrophoresis in the gaiter area of controls and patients with lipodermatosclerosis (LDS). Bars are median (interquartile range).* *P = *0·001 (Mann–Whitney* U *test)*

The rise in blood flux was calculated using the formula:

$$\text{Percentage rise in flux} = \frac{\text{peak flux} - \text{basal flux}}{\text{basal flux}} \times 100$$

The basal flux, peak flux following pilocarpine electrophoresis and percentage rise in flux were compared between the two groups using the Mann–Whitney *U* test.

Results

The basal blood flux, that following pilocarpine electrophoresis and the percentage rise in flux following electrophoresis are shown for the two groups in *Table 1*. The basal flux was significantly higher ($P = 0{\cdot}004$) in patients with lipodermatosclerosis than in controls. The percentage rise in flux in patients with lipodermatosclerosis was significantly lower ($P = 0{\cdot}001$) than in controls. However, the peak flux following pilocarpine electrophoresis was not significantly different between the two groups ($P = 0{\cdot}5$). These results are shown in *Figures 2* and *3*.

Discussion

Skin microcirculatory blood flow is capable of a large degree of change (0·3–150 ml per 100 mg tissue per min) depending on thermoregulation[11]. In cold conditions blood bypasses the upper layers of the dermis, avoiding heat loss and, as nutritive requirements of skin are low, skin damage is unusual.

A number of hypotheses have been proposed to explain the reduced hyperaemic capacity of liposclerotic skin in response to ischaemia and heating shown in previous studies. The inability of liposclerotic vessels to vasodilate beyond a certain degree may be due to the constricting effect of the pericapillary fibrin cuffs described by Burnand *et al.*[12]. This mechanism could operate in a similar manner to that seen in diabetic patients, in whom increased minimal vascular resistance in the skin of the leg caused by arteriolar hyalinosis has been demonstrated using an isotope washout technique[13]. Another possible explanation concerns the inability of the endothelium to react appropriately, possibly owing to damage by white cell activation and free radical release, which results in endothelial swelling and dysfunction[14].

The basal flux in the gaiter area in the present study was significantly higher in patients with lipodermatosclerosis than in controls. Similar findings using laser Doppler fluxmetry have been reported by a number of workers[2,3,15]. The increased flux

Table 1 *Basal laser Doppler flux and that following pilocarpine electrophoresis*

	Patients with lipodermatosclerosis ($n = 30$)*	Controls ($n = 20$)*	P†	95% confidence interval of difference
Basal flux (arbitrary units)	125 (72–277)	67 (60–82)	0·004	16–153
Peak flux (arbitrary units)	665 (382–1025)	765 (452–975)	0·5	−270 to 150
Rise in flux (%)	295 (74–633)	831 (535–1413)	0·001	263–750

*Values are median (interquartile range). †Mann–Whitney *U* test may be the result of chronic inflammation or an increased metabolic requirement of the skin. The significantly lower percentage rise in flux in liposclerotic skin in response to a vasodilatory stimulus shown in the present study is similar to that reported previously[3]. This suggests that the microcirculation has less reserve for response to stress such as injury. In this study the reduced percentage rise in flux is a reflection of the increased basal flux in liposclerotic skin.

The present results also show that the peak flux in the skin following a direct vasodilatory stimulus is the same in patients with chronic venous insufficiency and controls. This is contrary to previous findings when an indirect method of producing vasodilatation by heating the skin to 43–44°C was used. The explanation for the contradictory results may lie in the nature of the stimulus applied. In the present study the stimulus acted directly on the skin capillaries and so impairment of other mechanisms of vasodilatation did not influence results.

Impairment of the vasodilatory response to heating and ischaemia, but not to pilocarpine, suggests compromise of or damage to the indirect pathways of vasodilatation. This may indicate a peripheral neuropathy in chronic venous hypertension. Such an explanation would be consistent with previous findings of altered vasomotion characteristics in the skin of affected patients[16,17], and a C fibre neuropathy associated with chronic venous insufficiency[18,19].

References

1. Stibe E, Cheatle TR, Coleridge Smith PD, Scurr JH. Liposclerotic skin: a diffusion block or a perfusion problem? *Phlebology* 1990; **5**: 231–6.
2. Cheatle TR, Coleridge Smith PD, Scurr JH. Skin microcirculatory responses in chronic venous insufficiency: the effect of short-term venous hypertension. *Vasa* 1991; **20**: 63–9.
3. Cheatle TR, Stibe ECL, Shami SK, Coleridge Smith PD, Scurr JH. Vasodilatory capacity of the skin in venous disease and its relationship to transcutaneous oxygen tension. *Br J Surg* 1991; **78**: 607–10.
4. Tanner R, Cherry GW, Hale C, Ryan TJ. Impaired hyperaemic response in the microcirculation in patients with venous leg ulcers. *Br J Dermatol* 1989; **121**(Suppl 34): 45.
5. Clyne CAC, Ramsden WH, Chant ADB, Webster JHH. Oxygen tension on the skin of the gaiter area of limbs with venous disease. *Br J Surg* 1985; **72**: 644–7.
6. Kolari PJ, Pekanmaki K, Pohjola RT. Transcutaneous oxygen tension in patients with post-thrombotic leg ulcers: treatment with intermittent pneumatic compression. *Cardiovasc Res* 1988; **22**: 138–41.
7. Mannarino E, Pasqualine L, Maragoni G, Sanchini R, Regni O, Innocente S. Chronic venous incompetence and transcutaneous oxygen pressure: a controlled study. *Vasa* 1988; **17**: 159–61.
8. Mani R, White JE, Barrett DF, Weaver PW. Tissue oxygenation, venous ulcers and fibrin cuffs. *J R Soc Med* 1989; **82**: 345–6.
9. Greenburg S, Curro FA, Tanaka TP. Regulation of vascular smooth muscle of the microcirculation. In: Mortillaro NA, ed. *The Physiology and Pharmacology of the Microcirculation*. New York: Academic Press, 1983: 111.
10. Parkhouse N, Le Quesne PM. Impaired neurogenic vascular response in patients with diabetes and neuropathic foot lesions. *N Engl J Med* 1988; **318**: 1306–9.
11. Champion RH. Disorders of blood vessels. In: Champion RH, Burton JL, Elbing FJG, eds. *Textbook of Dermatology*. Oxford: Blackwell Scientific, 1992: 1827.
12. Burnand KG, Whimster I, Naidoo A, Browse NL. Pericapillary fibrin in the ulcer-bearing skin of the leg: the cause of lipodermatosclerosis and venous ulceration. *BMJ* 1982; **285**: 1071–2.
13. Kastrup J, Norgaard T, Parving H-H, Lassen NA. Increased minimal vascular resistance and arteriolar hyalinosis in skin on the leg in insulin-dependent diabetic patients. *Scand J Clin Lab Invest* 1987; **47**: 475–82.
14. Coleridge Smith PD, Thomas P, Scurr JH, Dormandy JA. Causes of venous ulceration: a new hypothesis. *BMJ* 1988; **296**: 1726–7.
15. Belcaro G, Rulo A, Vasdekis S, Williams MA, Nicolaides AN. Combined evaluation of postphlebitic limbs by laser Doppler flowmetry and transcutaneous P_{O_2}/P_{CO_2} measurements. *Vasa* 1988; **17**: 257–61.
16. Cheatle TR, Shami SK, Stibe E, Scurr JH, Coleridge Smith PD. Vasomotion in venous disease. *J R Soc Med* 1991; **84**: 261–3.
17. Chittenden SJ, Shami SK, Cheatle TR, Scurr JH, Coleridge Smith PD. Vasomotion in the leg skin of patients with chronic venous insufficiency. *Vasa* 1992; **21**: 138–42.
18. Ardron ME, Helme RD, McKernan S. Microvascular skin responses in elderly people with varicose leg ulcers. *Age Ageing* 1991; **20**: 124–8.
19. Shami SK, Farrah J, Fowler CJ, Scurr JH, Coleridge Smith PD. Chronic venous insufficiency causes C fibre neuropathy. *Br J Surg* 1991; **78**: 1506 (Abstract).

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Treatment of the axilla in patients with screen-detected breast cancer

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Management of the axillary lymph nodes in patients with screen-detected breast cancer is controversial. Optimal treatment should combine accurate determination of node status and avoidance of unnecessary morbidity. This study attempted to determine whether axillary node status could be accurately predicted using selected criteria in women with screen-detected breast cancer. Of 223 breast cancers excised in the Greater Manchester breast screening programme, 180 were invasive and 40 of these had associated lymph node metastases. The presence of involved nodes was associated with large tumour size, high tumour grade and the absence of mammographic microcalcification. Multiple logistic regression analysis revealed that each of these three factors was independently significant. Women with a screen-detected breast cancer <1 cm in diameter or those with grade I tumours <3 cm (35 per cent of the total) could be spared axillary surgery with an expected reduction in morbidity and operating time.

The value of level III axillary dissection has not been fully evaluated in patients with screen-detected breast cancer. It has been advocated by some as the preferred management in all patients with operable breast cancer to gain maximum prognostic information and ensure a low rate of axillary recurrence[1]. In patients with screen-detected cancer, the average tumour size is smaller and axillary node positivity less than in those with symptomatic lesions. To avoid axillary surgery with its attendant morbidity it would be rational to try to predict which patients have uninvolved axillae.

Some centres advocate axillary node sampling[2], and others have concluded that it is unreliable, because of low or no lymph node yield[3,4]. Accurate estimation of overall survival depends on the excision of an adequate number of lymph nodes[4]. Ten nodes is an optimum number to be sampled but unfortunately many surgeons excise fewer than this during level III dissection. The number of nodes recovered is also dependent on the thoroughness of the pathologist[5,6].

Two groups of patients from the breast-screening service can be identified: a group with palpable tumours who can be managed as if they had symptomatic breast cancer, and those with an impalpable tumour that is undetectable by ultrasonography and has to be identified by a localization procedure. In the latter group an appropriate surgical plan is difficult to formulate until histological proof of the mammographic abnormality has been obtained. It would be an advantage in these patients to have some indication of lymph node status before definitive surgery.

The aim of this study was to identify features of screen-detected breast cancer that could accurately predict node status, to enable preoperative selection for appropriate axillary surgery.

Patients and methods

A retrospective analysis was performed of all women treated by the Greater Manchester Breast Screening Service during the first 40 months of screening. Of women treated at the University Hospital of South Manchester, 223 were found to have malignant breast disease and 180 had invasive cancer. Therapeutic axillary dissection was performed in 160 patients; these women were analysed in detail.

Patients with a screen-detected invasive breast cancer underwent axillary dissection and wide local excision or mastectomy. Operation was performed following cytological diagnosis by fine-needle aspiration cytology (FNAC) or histopathological diagnosis based on needle or open biopsy, or ultrasonographic findings. Various factors have been assessed prospectively and incorporated into a patient database: pathological tumour size after formalin fixation, tumour grade and type (modified Bloom and Richardson grading system)[7], the presence or absence of microcalcification on the screening mammogram, previous benign or malignant breast biopsy, positive family history and the site of the primary tumour. Clinical and mammographic size were assessed to see whether they could be used as an accurate predictor of actual pathological size.

Statistical significance was assessed by the χ^2 test with Yates' correction and by multiple logistic regression analysis.

Results

Forty (25 per cent) of the 160 axillary dissections revealed positive lymph nodes. Twenty patients did not have axillary surgery: one had metastatic disease from the outset; one had an intracystic papillary neoplasm; eight had grade I medially placed tumours <1 cm in diameter; four who were unfit had lateral tumours of small size that were resected under local anaesthesia; and six had laterally placed tumours with such small areas of invasion (usually <5 mm) that full axillary surgery was not considered appropriate.

Pathological size of tumour

As the size of the primary cancer increased, so did the chance of having lymph node metastasis ($P < 0.0001$; *Figure 1*). Lymph node involvement ranged from one (3 per cent) positive axilla of 31 dissected for tumours <1 cm to 11 of 22 (50 per cent) in those with tumours ≥3 cm.

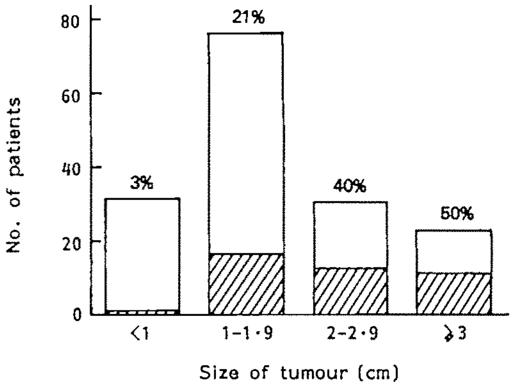

Figure 1 *Relationship between the pathological size of the primary tumour and axillary lymph node status. The percentage of patients with positive axillae is shown.* ☐, *No metastases;* ■, *metastases*

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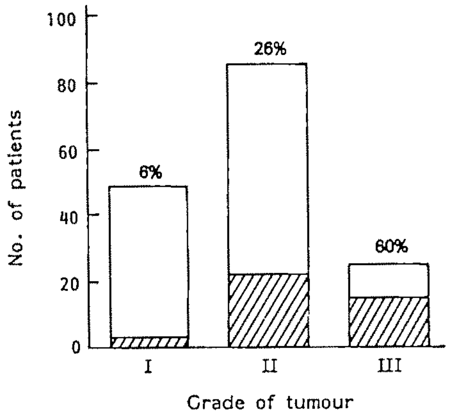

Figure 2 *Relationship between the pathological grade of the primary tumour and axillary lymph node status. The percentage of patients with positive axillae is shown.* □, *No metastases;* ■, *metastases*

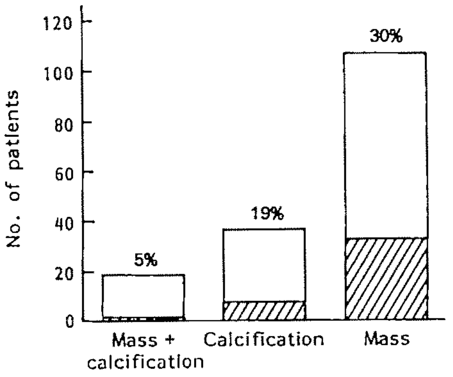

Figure 3 *Relationship between the presence of mammographic microcalcification and axillary lymph node status. The percentage of patients with positive axillae is shown.* □, *No metastases;* ■, *metastases*

Pathological grade and type of tumour

The poorer the differentiation of the tumour, the greater the frequency of axillary node metastasis ($P < 0{\cdot}0001$). Only 6 per cent of patients with grade I tumours had involved lymph nodes compared with 60 per cent of those with grade III (*Figure 2*). The type of tumour had no effect on the risk of lymph node metastasis. Ductal carcinomas were found in 33 (82 per cent) of 40 patients with positive nodes and in 93 (78 per cent) of 120 with negative nodes. Seven (18 per cent) of 40 patients in the node-positive and 19 (16 per cent) of 120 in the node-negative group had lobular carcinoma.

Lymph node involvement

Axillary node clearance yielded a mean of 19 (range 7–42) lymph nodes per axilla and the number of nodes containing metastases per patient ranged from one to 20. As size and grade of tumour increased, the proportion of involved nodes gradually increased. Thirteen patients had a single node involved, 18 had between two and four involved nodes, five had between five and ten, and four had more than ten.

For grade I tumours with axillary node metastasis, seven (16 per cent) of the 45 resected nodes contained tumour and this increased in grade III tumours to 60 (25 per cent) of the 244 resected nodes. For tumour size, the proportion of axillary nodes involved also gradually rose: all tumours <1 cm had only two (15 per cent) of 13 involved nodes and those $\geqslant 3$ cm had 50 (27 per cent) of 183 involved.

Microcalcification on the screening mammogram

Of screened patients undergoing axillary dissection, 55 (34 per cent) showed radiological microcalcification. The presence of mammographic microcalcification, alone or in the presence of a mass, was predictive for node negativity ($P = 0{\cdot}024$). When microcalcification alone was present, only 19 per cent of patients had axillary lymph node metastases; when it was associated with a mass or significant architectural distortion, the proportion with involved axillae fell to 5 per cent (*Figure 3*). Conversely, 30 per cent of patients with a mass but with no microcalcification had nodal metastases.

Clinical and mammographic prediction of actual pathological size and relationship to tumour position and palpability

Clinical size was assessable in 115 of the 180 patients, but was accurate to within 5 mm of the pathological size in only 37 (32 per cent). Mammographic size estimation was available in 125 patients and found to be accurate to within 5 mm in 64 (51 per cent). The prediction of pathological size from clinical or radiological size was therefore inaccurate and if size is to be used as an indicator of node status then only the pathological size will suffice.

The position of each mammographic abnormality was identified and a note made of whether or not the lesion was palpable. Tumour position bore no relationship to the possibility of axillary lymph node metastasis and 36 per cent of medial tumours had positive lymph nodes. Impalpable tumours were associated with positive axillary nodes in six (11 per cent) of 56 patients. Node-negative tumours were palpable in only 70 (58 per cent) of 120 cases, compared with node-positive lesions which were palpable in 34 (85 per cent) of 40. The same three factors were predictive for node positivity irrespective of the palpability of the primary tumour, which was itself independent of tumour size. None of the other factors studied had any value in the prediction of axillary node status.

Multivariate analysis

The data were subjected to multiple logistic regression analysis, which demonstrated that three factors, pathological tumour size ($P < 0{\cdot}001$), pathological tumour grade ($P < 0{\cdot}001$) and the absence of tumour microcalcification ($P < 0{\cdot}05$), were independently predictive for axillary node metastasis.

The relative risk for axillary node metastasis was 8·4 for each 1-cm increase in tumour size over a baseline of 1 cm. When grade was reviewed in a similar manner, grade II tumours had a relative risk for lymph node metastasis of 4·3 compared with grade I lesions, and this rose to 17·8 for grade III cancers.

Microcalcification had a relative risk of only 0·3, and hence the risk of lymph node metastasis was two-thirds lower in patients with than in those without mammographic microcalcification.

Discussion

Three clear predictors of positive axillary node status were identified: increasing pathological tumour size, worsening pathological tumour grade and absence of microcalcification. These could be of use in the management of the screened patient, when the primary tumour has been excised as a preliminary step, usually after needle or ultrasonographic localization biopsy.

Other authors[8–14] have reported the incidence of axillary node metastasis in patients with screen-detected breast cancer as being between 7 and 35 per cent. The finding of a progressive risk of lymph node metastasis with increasing tumour size in the present study confirms the work of others[12–14]. The observation that mammographically detected breast cancers that are palpable are associated with increased node positivity has been reported previously[15].

In patients with screen-detected breast cancer, the axilla may not require dissection, but this needs to be considered in the light of tumour grade and type. The patient with a screen-detected breast cancer should be offered full axillary dissection only if there is a high probability of lymph node metastasis.

The mean number of lymph nodes dissected per axillary clearance in the present study is in keeping with values reported in previous large series[16,17], and a plan of management of potentially node-negative disease can be formulated. A patient with a tumour <1 cm of any grade, or a grade I cancer <3 cm, with microcalcification on the screening mammogram and an impalpable lesion has a negligible risk of lymph node disease. Using the three statistically significant factors, one-third of patients in the present study could have avoided extensive axillary surgery. The choice of diagnostic axillary surgery for patients with a low risk of nodal involvement varies. They could be assumed to have no nodal disease and be spared any intervention in the axilla. They could undergo level I clearance if there is a small risk of nodal disease, ensuring that ten lymph nodes are removed, with the resulting decrease in operating time. Adjuvant therapy could be planned on the results. Patients with >10 per cent chance of lymph node metastasis could be offered level III clearance. The quality-assurance guidelines laid down for surgeons undertaking breast screening work advise that axillary surgery of some type ought to be performed.

Positive cytology of mammographic abnormalities does not prove invasive malignancy; histopathological diagnosis is preferable, to prevent unnecessary axillary surgery in patients with ductal carcinoma *in situ*. Currently, the majority of screened patients with impalpable mammographic abnormalities do not undergo stereotactic FNAC, and the present guidelines will be valuable for the treatment of these women.

The failure to obtain any lymph nodes from axillary node sampling occurs in 25 per cent of cases; in many patients a single node is found which fails to provide useful information[18,19]. The probability of detecting node positivity increases with the number of nodes removed, up to a maximum of ten nodes[6].

A recent overview[20] has suggested that perimenopausal and postmenopausal women with heavy nodal involvement benefit from adjuvant chemotherapy. Failure to stage the patients correctly will result in a proportion not receiving the most appropriate adjuvant therapy. A blanket policy of adjuvant therapy would overtreat some 60 per cent of patients who are node negative with small screen-detected tumours.

In centres where stereotactic FNAC is not available, the true screen-detected breast cancer (i.e. one that is impalpable and demonstrable only by its radiological abnormality) will have to be treated by a two-stage surgical procedure. The initial approach is to establish a histological diagnosis by localization biopsy and then to plan axillary surgery with the knowledge of all three predictive indices. Up to 35 per cent of patients will not require any further surgical intervention and will therefore be spared unnecessary surgery.

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References

1. Fentiman IS, Mansel RE. The axilla: not a no-go zone. *Lancet* 1991; **337**: 221–3.
2. Steele RJC, Forrest APM, Gibson T *et al.* The efficacy of lower axillary sampling in obtaining lymph node status in breast cancer: a controlled randomized trial. *Br J Surg* 1985; **72**: 368–9.
3. Senofsky GM, Moffat FL Jr, Davis K *et al.* Total axillary lymphadenectomy in the management of breast cancer. *Arch Surg* 1991; **126**: 1336–41.
4. Benson EA, Thorogood J. The effect of surgical technique on local recurrence rates following mastectomy. *Eur J Surg Oncol* 1986; **12**: 267–71.
5. O'Dwyer PJ. Axillary dissection in primary breast cancer. *BMJ* 1991; **302**: 360–1.
6. Graversen HP, Bilchert-Toft M, Anderson JA, Zedeler K. Breast cancer: risk of axillary recurrence in node negative patients following partial dissection of the axilla. *Eur J Surg Oncol* 1988; **14**: 407–12.
7. Bloom HJG, Richardson WW. Histological grading and prognosis in breast cancer. A study of 1409 cases of which 359 have been followed for 15 years. *Br J Cancer* 1957; **11**: 359–77.
8. Schwartz GF, Feig SA, Rosenberg AL *et al.* Staging and treatment of clinically occult breast cancer. *Cancer* 1984; **53**: 1379–84.
9. Meyer JE, Kopans DB, Stomper PC, Lindfors KK. Occult breast abnormalities: percutaneous preoperative needle localisation. *Radiology* 1984; **150**: 335–7.
10. Gamagami P, Colburn WJ, Gierson ED, Silverstein MJ. Nonpalpable breast lesions: diagnosis with slightly overpenetrated screen-film mammography and hook wire-directed biopsy in 1014 cases. *Radiology* 1989; **171**: 633–8.
11. Margolis DS, McMillen MA, Hashimi H *et al.* Aggressive axillary evaluation and therapy for nonpalpable carcinoma of the breast. *Surg Gynecol Obstet* 1992; **174**: 109–13.
12. Tinnemans JG, Wobbes T, Holland R *et al.* Treatment and survival of female patients with nonpalpable breast carcinoma. *Ann Surg* 1989; **209**: 249–53.
13. Anderson TJ, Lamb J, Donnan P *et al.* Comparative pathology of breast cancer in a randomised trial of screening. *Br J Cancer* 1991; **64**: 108–13.
14. Duffy SW, Tabar L, Fagerberg G *et al.* Breast screening, prognostic factors and survival – results from the Swedish two county study. *Br J Cancer* 1991; **64**: 1133–8.
15. Bassett LW, Liu TH, Giuliano AE, Gold RH. The prevalence of carcinoma in palpable *vs* impalpable, mammographically detected lesions. *AJR Am J Roentgenol* 1991; **157**: 21–4.
16. Veronesi U, Luini A, Galimberti V *et al.* Extent of metastatic axillary involvement in 1446 cases of breast cancer. *Eur J Surg Oncol* 1990; **16**: 127–33.
17. Rosen PP, Lesser ML, Kinne DA, Beattie EJ. Discontinuous or 'skip' metastases in breast carcinoma. *Ann Surg* 1983; **197**: 276–83.
18. Forrest APM, Stewart HJ. Simple mastectomy and axillary node sampling in the management of primary breast cancer. *Ann Surg* 1982; **196**: 371–8.
19. Davies GC, Mills RR, Haywood JL. The incidence of error with axillary node biopsy. *Ann Surg* 1980; **192**: 145–51.
20. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. *Lancet* 1992; **339**: 1–15, 71–85.

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Symptomatic outcome after laparoscopic cholecystectomy

To evaluate the symptomatic outcome after laparoscopic cholecystectomy, a standard symptom questionnaire was sent to three patient groups at least 1 year after surgery: 115 patients had undergone laparoscopic cholecystectomy; 200 had undergone open cholecystectomy; and 200 had had inguinal hernia repair. Return of questionnaires was higher after laparoscopic cholecystectomy (100 of 115; 87·0 per cent) than the open procedure (167 of 200; 83·5 per cent) or hernia repair (163 of 200; 81·5 per cent). There was no difference in the number of patients who considered the operation to have cured or improved their preoperative symptoms after laparoscopic cholecystectomy (94 of 100; 94·0 per cent), open cholecystectomy (157 of 167; 94·0 per cent) or hernia repair (154 of 163; 94·5 per cent). Similar numbers considered their operation to have been a success (94·0, 95·2 and 94·5 per cent respectively). The prevalence of abdominal pain, nausea, flatulence, food intolerance and heartburn was similar in all groups of patients following operation. Diarrhoea occurred more often following laparoscopic (6·0 per cent) and open (4·2 per cent) cholecystectomy than hernia repair (1·2 per cent). Patients who underwent laparoscopic cholecystectomy tended to have a higher incidence of nausea or vomiting than those undergoing the open procedure, and consumed significantly more antacids (23·0 versus *12·0 per cent,* $P < 0·02$*). Laparoscopic cholecystectomy achieved the same rate of patient satisfaction as open cholecystectomy, with no apparent symptomatic advantage.*

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Laparoscopic cholecystectomy has become the preferred technique for treatment of symptomatic gallbladder stones[1]. Published series have documented mortality, morbidity (particularly bile duct injury), time in hospital and time off work[2–6]. There are no studies on the symptomatic outcome following this procedure apart from that of Peters *et al.*[7], who reported a 3-month follow-up in 52 patients who underwent elective laparoscopic cholecystectomy. Overall, 77 per cent of patients considered their symptoms to be cured and the remainder, with one exception, were improved by surgery.

Symptoms are the indication for the procedure in the majority of patients and it therefore seemed appropriate to assess the symptomatic outcome after laparoscopic cholecystectomy and compare it with that after the conventional open procedure and, as a control, inguinal hernia repair.

Patients and methods

A standard symptom questionnaire (*Appendix 1*) was sent to 115 patients who had undergone laparoscopic cholecystectomy at least 12 months previously (mean follow-up 14·0 months). The questionnaire was based on that used to assess outcome after surgery for duodenal ulcer and gastro-oesophageal reflux[8,9] and modified after Bates *et al.*[10] to include questions appropriate to cholecystectomy. An identical questionnaire was sent to 200 patients who had undergone open cholecystectomy > 12 months previously (mean follow-up 28·4 months) and to a further 200 who had had inguinal hernia repair at least 12 months previously (mean follow-up 31·4 months).

Patients were asked to indicate whether in the preceding 6 months they had experienced the listed symptoms 'every day', 'most days', 'occasionally' or 'never'. They were asked about appetite, enjoyment of food and specific food intolerance, and whether they had consulted their general practitioner (GP) regarding stomach pain since the operation and, if so, to give the reasons. Assessment of the operation in terms of 'cured', 'improved', 'same' or 'worse' was requested from patients, and they were asked whether they felt the operation had been successful.

Table 1 *Mode of presentation of patients undergoing laparoscopic or open cholecystectomy*

	Laparoscopic cholecystectomy ($n = 100$)	Open cholecystectomy ($n = 167$)
Acute cholecystitis	34·0	36
Biliary pain	42·0	34
Chronic dyspepsia	13·0	15
Choledocholithiasis	4·0	5
Empyema	5·0	6
Pancreatitis	2·0	4

Values are percentages

Details of preoperative symptoms and indications for the procedure had been recorded prospectively on a standard pro forma for patients undergoing laparoscopic cholecystectomy.

The mode of initial presentation of patients undergoing laparoscopic and open cholecystectomy is shown in *Table 1*. Those with choledocholithiasis had the duct stones treated endoscopically before proceeding to cholecystectomy when indicated.

Information from returned questionnaires was entered into a microcomputer and analysed. Confidence intervals were calculated using Confidence Interval Analysis (British Medical Association, London, UK) software[11].

Results

Return of questionnaires was higher after laparoscopic cholecystectomy (100 of 115; 87·0 per cent) than open cholecystectomy (167 of 200; 83·5 per cent) or hernia repair (163 of 200; 81·5 per cent). The mean (95 per cent confidence interval (c.i.)) age of patients undergoing laparoscopic (52·8 (49·6–55·3) years) or open (53·2 (51·2–55·4) years) cholecystectomy was similar, although the inguinal hernia group was on average 7 years older (mean 59·6 (95 per cent c.i. 57·4–62·1) years), with a greater proportion of men. The proportion of

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Table 2 *Symptoms experienced every day or most days at a minimum of 1 year after surgery*

	Laparoscopic cholecystectomy ($n = 100$)	Open cholecystectomy ($n = 167$)	Inguinal hernia repair ($n = 163$)
Symptom			
Abdominal pain	6·0 (2·2–12·6)	6·6 (3·3–11·5)	6·1 (3·0–11·0)
Nausea and/or vomiting	10·0 (4·9–17·6)	3·6 (1·3–7·7)	4·9 (2·1–9·4)
Heartburn	14·0 (7·9–22·4)	9·6 (5·6–15·1)	10·4 (5·7–15·1)
Bloating	12·0 (6·4–20·0)	14·4 (9·1–19·7)	4·9 (2·1–9·4)
Flatulence	17·0 (10·2–25·8)	20·4 (14·3–26·5)	14·1 (8·8–19·5)
Diarrhoea	6·0 (2·2–12·6)	4·2 (1·7–8·4)	1·2 (0·2–4·4)
Antacid consumption	23·0 (15·2–32·5)*	12·0 (7·1–16·9)	15·3 (9·8–20·9)

Values are percentages (95 per cent confidence interval). *$P < 0·02$ (laparoscopic cholecystectomy *versus* open cholecystectomy and inguinal hernia repair groups, χ^2 test, 95 per cent confidence interval of difference 1·4–20·6 per cent)

Table 3 *Patient assessment of appetite, enjoyment of food and food intolerance following operation*

	Laparoscopic cholecystectomy ($n = 100$)	Open cholecystectomy ($n = 167$)	Inguinal hernia repair ($n = 163$)
Good appetite	88·0 (80·0–93·6)	88·0 (83·1–92·9)	96·9 (93·0–99·0)
Enjoyment of food	89·0 (81·2–92·9)	94·6 (90·0–97·5)	97·5 (93·8–99·3)
Food intolerance	42·0 (32·2–52·3)	46·7 (44·5–59·7)	26·3 (19·1–32·5)

Values are percentages (95 per cent confidence interval)

Table 4 *Patient assessment of outcome following operation*

	Laparoscopic cholecystectomy ($n = 100$)	Open cholecystectomy ($n = 167$)	Inguinal hernia repair ($n = 163$)
'Cured' or 'improved'	94·0 (87·4–97·8)	94·0 (89·3–97·1)	94·5 (89·9–97·4)
Operation a success	94·0 (87·4–97·8)	95·2 (90·8–97·9)	94·5 (89·8–97·4)

Values are percentages (95 per cent confidence interval)

Table 5 *Current symptoms experienced every day or most days and patient assessment according to preoperative presentation for laparoscopic cholecystectomy*

	Preoperative symptoms	
	Acute ($n = 64$)	Chronic ($n = 36$)
Current symptoms		
Stomach pain	2 (3)	4 (11)
Heartburn	5 (8)	9 (25)
Nausea and/or vomiting	4 (6)	6 (17)
Flatulence	10 (16)	8 (22)
Outcome		
Success	59 (92)	28 (78)
Symptoms cured or improved	61 (95)	30 (83)

Values in parentheses are percentages

patients having symptoms every day or most days following each of the operations is shown in *Table 2*. There were no significant differences between the laparoscopic and open procedures for any symptom.

Results of questions on appetite, enjoyment of food and food intolerance are shown in *Table 3*.

The number of patients who consulted a GP following laparoscopic cholecystectomy, 23 of 100 (23·0 per cent (95 per cent c.i. 15·2–32·5 per cent)), was higher than that after open cholecystectomy, 31 of 167 (18·6 per cent (95 per cent c.i. 12·1–24·5 per cent)), or hernia repair, 22 of 163 (13·5 per cent (95 per cent c.i. 8·2–18·7 per cent)), but these differences were not significant.

Patient assessment of the operation is shown in *Table 4*.

The prevalence of smoking was similar in the three groups (laparoscopic cholecystectomy, 26 of 100; open cholecystectomy, 41 of 167; hernia repair, 38 of 163).

The proportion of patients experiencing specific symptoms every day or most days following laparoscopic cholecystectomy is shown in *Table 5*, according to the acute or chronic nature of preoperative symptoms.

Discussion

Cholecystectomy is indicated only when gallstones give rise to symptoms[12], which was the case in all patients in the present series.

Studies that have assessed symptomatic outcome after open cholecystectomy have given differing results. Johnson[13] found that after the open procedure 46 per cent of patients were free from flatulent dyspepsia but 30 per cent were no better. Ros and Zambon[14] evaluated 93 patients before and 2 years after cholecystectomy, at which time only 53 per cent were found to be completely symptom-free. In most of these patients the indication for operation had been flatulent dyspepsia. The present study showed that 17·0 per cent of patients had flatulence every day or most days after laparoscopic cholecystectomy compared with 20·4 per cent after the open procedure. Antacid consumption was noted particularly after laparoscopic cholecystectomy, and is presumably an attempt to treat the heartburn, which in this series was present every day or most days in 14·0 per cent of patients who underwent this procedure. The similar prevalence of these and other symptoms such as stomach pain and visits to a GP in the control group is in keeping with previous observations on hernia operations[15] and the general population[16]. It can be assumed that the prevalence of symptoms in patients following cholecystectomy will be similar.

Bates *et al.*[10] assessed 274 patients before and 1 and 2 years after open cholecystectomy and found that at 1 year 23 per cent of patients had nausea, 34 per cent abdominal pain, 37 per cent distension, 43 per cent indigestion and 44 per cent flatulence. These differences may reflect the different wording in questionnaires, but only 6·6 per cent of the patients in the present study had abdominal pain every day or most days following cholecystectomy. Bates *et al.*[10] observed no change in symptomatic outcome between the first and second postoperative years. It was felt appropriate in the present study to survey patients undergoing open cholecystectomy in the year ending May 1990 and those undergoing laparoscopic cholecystectomy in the year beginning January 1990, and all patients were asked about symptoms in the preceding 6 months.

Previous studies have found that chronic pain in the abdominal wound was the major source of abdominal pain following open cholecystectomy in from 24 per cent[14] to 27 per cent[17] of patients. Patients in the present series were not asked to specify whether the pain was wound related, but the similar incidence of pain for open and laparoscopic procedures suggests that wound-related problems were not a major contribution.

The results of the present study are similar to those of Gunn and Keddie[17], who found that pain was relieved by cholecystectomy in 77 per cent of patients and improved in a further 16 per cent.

The higher proportion of patients presenting with acute symptoms in the present series may help to account for the better results compared with those of Ros and Zambon[14] and Bates *et al.*[10].

Overall, 94·0 per cent of patients considered laparoscopic cholecystectomy a success and 94·0 per cent felt their initial problem had been cured or improved. The postulated long-term benefits of laparoscopic over open cholecystectomy, such as fewer wound-related symptoms[6], do not seem to have been borne out. In this study laparoscopic cholecystectomy achieved the same rate of patient satisfaction as open cholecystectomy and none of the specific symptoms was different at a minimum of 1 year after each operation.

References

1. Holohan TV. Laparoscopic cholecystectomy. *Lancet* 1991; **338**: 801–3.
2. Cuschieri A, Dubois F, Mouiel J *et al.* The European experience with laparoscopic cholecystectomy. *Am J Surg* 1991; **161**: 385–7.
3. Zucker KA, Bailey RW, Gadacz TR *et al.* Laparoscopic guided cholecystectomy. *Am J Surg* 1991; **161**: 36–44.
4. Meyers WC, Branum GD, Farouk M *et al.* A prospective analysis of 1518 laparoscopic cholecystectomies. *N Engl J Med* 1991; **324**: 1073–8.
5. Vitale GC, Collet D, Larson GM *et al.* Interruption of professional and home activity after laparoscopic cholecystectomy among French and American patients. *Am J Surg* 1991; **161**: 396–8.
6. Brookes DC, Becker JM, Carr-Locke DL. Laparoscopic cholecystectomy. *Baillieres Clin Gastroenterol* 1991; **5**: 225–38.
7. Peters JH, Ellison C, Innes J *et al.* Safety and efficacy of laparoscopic cholecystectomy. A prospective analysis of 100 initial patients. *Ann Surg* 1991; **213**: 3–12.
8. Macintyre IMC, Millar A, Smith AN, Small WP. Highly selective vagotomy 5–15 years on. *Br J Surg* 1990; **77**: 65–9.
9. Macintyre IMC, Goulbourne IA. Long term results after fundoplication: a 5–15 year review. *J R Coll Surg Edinb* 1990; **35**: 159–62.
10. Bates T, Ebbs SR, Harrison M, A'Hern RP. Influence of cholecystectomy on symptoms. *Br J Surg* 1991; **78**: 964–7.
11. Gardner MJ, Altman DG. *Statistics with Confidence*. London: British Medical Journal, 1990.
12. Finlayson N. Cholecystectomy for gall stones. *BMJ* 1989; **298**: 133–4.
13. Johnson AG. Gall stones and flatulent dyspepsia; cause or coincidence? *Postgrad Med J* 1971; **47**: 767–72.
14. Ros E, Zambon D. Post-cholecystectomy symptoms. A prospective study of gall stone patients before and two years after surgery. *Gut* 1987; **28**: 1500–4.
15. Salaman JR, Harvey J, Duthie HL. Importance of symptoms after highly selective vagotomy. *BMJ* 1981; **283**: 1438.
16. Hannay DR. Symptom prevalence in the community. *J R Coll Gen Pract* 1978; **28**: 492–9.
17. Gunn A, Keddie N. Some clinical observations on patients with gall stones. *Lancet* 1972; **ii**: 239–41.

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Appendix 1 *Patient questionnaire*

Date: Record no.:

In this questionnaire you will be asked about your symptoms. Read each item and circle the answer which applies best to you.

The questions relate to how you have been feeling over *the last 6 months only.*

I have had stomach pain:	Every day/Most days/Occasionally/Never
I have had nausea:	Every day/Most days/Occasionally/Never
I have vomited:	Every day/Most days/Occasionally/Never
I have had heartburn:	Every day/Most days/Occasionally/Never
I have felt bloated (bagged up):	Every day/Most days/Occasionally/Never
I have had belching:	Every day/Most days/Occasionally/Never
My bowels move:	.... times a day
I take antacids (e.g. Aludrox, Maalox, Gaviscon, Asilone, Mucaine, Gastrocote, Rennies, BiSoDoL, Tagamet, Zantac, Losec):	Every day/Most days/Occasionally/Never
I have had jaundice:	Yes/No
I have had diarrhoea:	Every day/Most days/Occasionally/Never
My appetite is:	Poor/Good
In general I enjoy my food:	Yes/No
Does any food 'disagree' with you?:	Yes/No (if Yes specify ....)
In the last 6 months I have consulted my own family doctor because of stomach pain:	Yes/No
Please add any additional comments:	....
Since operation my original problem has been:	Cured/Improved/Same/Worse
My operation has been a success:	Yes/No
Alcohol:	I don't drink alcohol/Would like to drink but cannot/Drink alcohol as I want

Please state how many cigarettes you smoke per day: .... cigarettes a day

Please list any hospital admissions since your operation:

Date	Hospital	Problem

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Expression of p53 in colorectal cancer and dysplasia complicating ulcerative colitis

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An immunohistochemical method using Pab1801, a monoclonal antibody specific to the human p53 protein, was applied to detect p53 expression in colorectal cancer and dysplasia complicating ulcerative colitis. Of 20 tissue samples with dysplasia, six showed positive immunoreactivity. Archival paraffin-embedded tissue blocks from 21 colitic cancers were analysed; 11 showed positive immunoreactivity, compared with ten of 21 samples from matched sporadic colorectal cancers (P *not significant*)*. Previous data suggesting that colorectal carcinoma complicating ulcerative colitis has a reduced frequency of c-Ki-*ras *mutation compared with sporadic cancer have led to the hypothesis that different genetic lesions underlie colitic and sporadic colorectal carcinoma. The present results suggest that this is not the case with regard to p53 gene alterations.*

Patients suffering from ulcerative colitis are at increased risk of developing colorectal cancer[1]. Carcinoma in ulcerative colitis almost always develops in areas of mucosal dysplasia, unlike sporadic colorectal cancer which develops from adenomatous polyps[2]. The incidence of c-Ki-*ras* mutations in ulcerative colitic carcinoma is 24 per cent and it would seem that mutations in this gene occur less frequently in such carcinomas than in sporadic colorectal cancers[3]. The differing modes of development and difference in genetic mutations so far demonstrated suggest that dissimilar genetic alterations underlie the development of colorectal cancer in these two situations.

The p53 gene product is a 53-kDa nuclear protein believed to regulate entry into and progression through the normal cell cycle[4]. It is induced during transition from G0 to G1 and is present at low levels in most normal fetal and adult tissue[5]. This protein is expressed by a gene located on the p arm of chromosome 17. Alterations of the p53 gene appear to be the most frequent mutation in human cancers, raised p53 expression being seen in many human tumours including colorectal carcinoma[6]. Work by van den Berg *et al.*[7] has described the immunohistochemical detection of p53 in 55 per cent of colorectal cancers and various groups have attempted to assess its prognostic significance[8,9].

The present study used an immunohistochemical technique to detect p53 expression in colorectal carcinoma arising in ulcerative colitis and compared the incidence of expression with that in a matched group of sporadic colorectal cancers. The frequency of p53 expression in a series of samples with epithelial dysplasia in ulcerative colitis and in ulcerative colitis with neither cancer nor dysplasia was also determined using the same technique.

Patients and methods

Patients were identified from the records of the Institute of Pathology at The Royal London Hospital. Sections were cut from formalin-fixed paraffin-embedded biopsies or from tissue blocks from colectomy or proctocolectomy specimens. Samples were incubated with Pab1801 (Oncogene Science, Uniondale, New Jersey, USA) using the following method. Sections 2–5 μm thick were cut from the tissue block and picked up on 3-aminopropyltriethoxysilane-coated slides[10]. After dewaxing and rehydration, sections were washed in Tris-buffered saline (TBS) at pH 7·4 with 0·1 per cent Triton X-100 (Sigma Chemicals, Poole, UK) and incubated for 20 min with 1:50 normal horse serum in 0·1 per cent bovine serum albumin (BSA) and then for 1 h with Pab1801 diluted 1:60 with 0·1 per cent BSA in TBS. Endogenous peroxidase was blocked by incubation for 30 min in 3 per cent hydrogen peroxide in TBS with 0·1 per cent Triton X-100 before the sections were incubated for 30 min in biotinylated horse antimouse immunoglobulin G (Vector Laboratories, Peterborough, UK) diluted 1:100 with 0·1 per cent BSA in TBS. After repeat washing with 3 per cent hydrogen peroxide in TBS, the sections were incubated with ABC reagent (Vector Laboratories)[11] for 30 min, washed with TBS and visualized with 3,3′-diaminobenzine tetrahydrochloride[12] for 7 min. Counterstaining with Carazzi's haematoxylin was followed by mounting in DPX (BDH, Poole, UK).

A tumour with an identified mutation at the p53 locus known to show consistently strong immunoreactivity with the p53 antibody was used as a positive control. Histologically normal mucosa from the resection margins of lengths of surgically removed colon served as a negative control. Additionally, a proportion of each batch of sections stained was not treated with primary antibody to confirm that any staining obtained was specific and not artefactual.

Sections were reviewed by an experienced histopathologist with no knowledge of the cases. The primary diagnosis of ulcerative colitis was confirmed and in no case was there evidence that Crohn's disease might be the primary diagnosis. Dysplasia was classified according to standard criteria[13] into high or low grade.

Results

Patients

A total of 21 patients with colorectal cancer in ulcerative colitis between 1954 and 1990 were identified: seven men and 14 women. The mean age at which the tumour was diagnosed was 58 (range 39–76) years. The Dukes' stage and histological grade of the tumours are shown in *Table 1*. Seven patients had associated areas of dysplasia.

Each tumour occurring in ulcerative colitis was matched as closely as possible with a sporadic cancer of similar grade and Dukes' stage from a patient of similar age and sex (*Table 1*). The mean age of this control group was 64 (range 42–79) years; there were 12 men and nine women.

Table 1 *Dukes' stage and tumour grade for sporadic colorectal cancer and that arising in ulcerative colitis*

	Well or moderately differentiated		Poorly differentiated	
Dukes' stage	Ulcerative colitis	Sporadic	Ulcerative colitis	Sporadic
A	4	4	0	0
B	4	4	3	3
C	5	5	5	5

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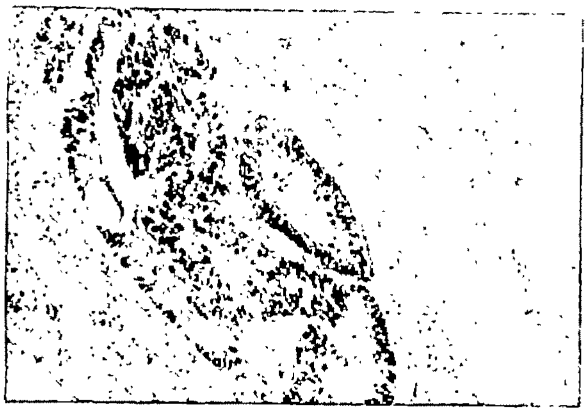

Figure 1 *Selective nuclear staining by p53 protein detection using Pab1801 in a colonic carcinoma complicating ulcerative colitis. (Original magnification ×250)*

Twenty patients with epithelial dysplasia in ulcerative colitis were identified; dysplasia in 11 was high grade and in nine low grade. These 20 include the seven with colitic cancer who had associated areas of dysplasia. A further 20 patients with ulcerative colitis but neither dysplasia nor cancer were also studied to determine whether colitic mucosa expressed p53.

Immunohistochemistry

There was no positive immunoreactivity in any of the negative controls, nor in any of the 20 samples of ulcerative colitis uncomplicated by dysplasia or cancer. The p53 protein was detected by positive nuclear staining in 11 of the 21 samples of colorectal carcinoma arising in ulcerative colitis (*Figure 1*). One tumour showed only strong focal immunoreactivity whereas the remainder showed diffuse reactivity that was weak in four specimens, weak with strong focal areas in two and strongly diffuse in four. Of the 21 sporadic colorectal cancer samples, ten showed positive immunoreactivity. There was no significant difference in the frequency of positive staining between colitic and sporadic cancers ($\chi^2 = 0{\cdot}095$, 1 d.f., $P > 0{\cdot}05$). Six of the 20 samples with dysplasia in ulcerative colitis showed positive staining; five of the positive specimens were high-grade dysplasia and one was of low grade.

Areas of mucosal dysplasia were seen in seven cancer samples; one positively stained cancer had associated areas of high-grade dysplasia that also showed positive staining. Sigmoidoscopic biopsies or resection specimens showing dysplasia were available from ten patients; two of these had low-grade dysplasia and showed no positive staining and eight had high-grade dysplasia, four of which showed positive immunoreactivity. Three patients with ulcerative colitis had dysplasia diagnosed at screening colonoscopy; one underwent two successive endoscopies with progression from low- to high-grade dysplasia. Of 22 biopsies obtained at colonoscopy, one showed positive staining; the p53-positive biopsy was one of five taken at colonoscopy from one patient with low-grade dysplasia.

Discussion

The development of colorectal cancer in patients suffering from ulcerative colitis has been described by many authors since the original observation by Crohn and Rosenberg[14] in 1925. The increased risk of developing this cancer is most marked in patients with total or extensive colitis over a prolonged period and an early age of onset[15]. There are a number of differences in the causation, development and outcome of carcinoma developing in ulcerative colitis compared with sporadic cancer. The most important difference is the development of mucosal dysplasia in ulcerative colitis; this may be macroscopically featureless or a flat plaque[2]. High-grade dysplasia is regarded as a precancerous condition, although cancer can develop in the absence of dysplasia or in parts of the colon seemingly unaffected by dysplasia[1,16,17]. Sporadic colorectal cancer develops from adenomatous polyps[18], but these are uncommon in ulcerative colitis[2]. Furthermore, the distribution of cancers in ulcerative colitis differs from that in sporadic cases, with a more even spread throughout the colon rather than the preponderance of rectosigmoid tumours found in the general population[19]. All series show that multiple cancers are seen more frequently in ulcerative colitis. The age at which cancer is diagnosed in this group is also lower than in the general population[20].

Clinical and histological evidence for a differing tumour biology in colitic cancer is supported by recent findings on the molecular biology of these tumours. Mutations in c-Ki-*ras* are found in 44–48 per cent of sporadic colorectal tumours[21,22]. Three groups have examined the incidence of c-Ki-*ras* mutations in colorectal cancer arising in ulcerative colitis. Melzer *et al.*[23] found one of four cancers contained a c-Ki-*ras* mutation while Burmer and colleagues[24] reported such mutation in only one of eight. Bell *et al.*[3] found that eight of 33 tumours in ulcerative colitis contained c-Ki-*ras* mutations compared with 14 of 33 sporadic controls in a case-matched series. These data suggest that c-Ki-*ras* mutations are found less commonly in colitic than sporadic cancers.

Another mutation frequently detected in colorectal and other malignancies is at the p53 locus on chromosome 17. The product p53 is a nuclear DNA-binding phosphoprotein that is expressed in virtually all cells. It has a short half-life and appears to have an important role in the regulation of cell proliferation. Studies of p53 expression in cultured cells show that increased levels are associated either with an abnormal mutated protein[25] or stabilization of the protein in a complex with viral antigens[26]. The presence of raised protein levels can therefore be used as a marker for mutated p53 and several antibodies that permit detection of abnormal p53 expression are now available.

Abnormal p53 expression is detected by immunohistochemical methods in up to 55 per cent of sporadic colorectal tumours[7,8]. This compares with a frequency of allelic deletion of the p53 locus in 75 per cent of colorectal cancers[21]. In contrast, adenomatous polyps have an incidence of p53 mutations of 8–20 per cent[7,21]; these alterations are seen in polyps with epithelial dysplasia, although the p53-positive areas are histologically indistinguishable from neighbouring negative regions[7]. Alterations at the p53 locus may be important in progression from a non-malignant phenotype to carcinoma. The present finding of abnormal p53 expression in 52 per cent of cancers in ulcerative colitis suggests that in this respect these tumours do not differ from their sporadic counterparts, despite other differences in molecular biology. It would seem that the two subsets of colorectal cancer have this pathway of tumour development in common, whereas a significant proportion of colitic cancers undergoes an as yet unidentified genetic alteration that can effect similar actions to the c-Ki-*ras* mutation.

Positive immunoreactivity was found for p53 in six of 20 samples showing epithelial dysplasia, five of which were of high grade. Allelic loss of the p53 gene has been demonstrated in cases of dysplasia in ulcerative colitis[27,28] and it may be that the loss of a p53 allele is a marker of progression to carcinoma.

From the data presented, the practical application of an immunohistochemical technique for detecting p53 expression in biopsies obtained at screening colonoscopy appears to be limited. Of 22 biopsies obtained in four colonoscopies, only one showed immunoreactivity. However, in three of the four colonoscopic examinations only low-grade dysplasia was present; five of a total of 11 instances of high-grade dysplasia were positive for p53 in the present study. Moreover, colonoscopic biopsies are small and, in large tumours and the larger specimens with dysplasia, staining tends to be patchy and discontinuous. It may be that, with larger biopsies or a greater number of samples, areas of positive immunoreactivity might be included. The significance of one instance of immunopositivity in a case of low-grade dysplasia is unclear;

in a recent study, loss of heterozygosity for p53 was seen in specimens of low-grade dysplasia and in mucosa negative for dysplasia in ulcerative colitis[29]. It may be that the presence of dysplasia and positive immunoreactivity for p53 in a biopsy specimen should prompt the clinician to regard the case with a higher degree of suspicion. This possibility should be clarified by testing biopsies obtained at successive colonoscopies in a larger group of patients.

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References

1. Lennard-Jones JE, Morson BC, Ritchie JK, Shove DC, Williams CB. Cancer in colitis: assessment of the individual risk by clinical and histological criteria. *Gastroenterology* 1977; **73** 80–9.
2. Morson BC, Pang LSC. Rectal biopsy as an aid to cancer control in ulcerative colitis. *Gut* 1967; **8**: 423–34.
3. Bell SM, Kelly SA, Hoyle JA *et al.* c-Ki-*ras* mutations in dysplasia and carcinomas complicating ulcerative colitis. *Br J Cancer* 1991; **64**: 174–8.
4. Mercer EW, Nelson D, DeLeo AB, Old LJ, Baserga R. Microinjection of monoclonal antibodies to p53 inhibits serum induced DNA synthesis. *Proc Natl Acad Sci U S A* 1982; **79**: 6309–12.
5. Rogel A, Popliker M, Webb CG, Oren M. p53 cellular tumor antigen: analysis of mRNA levels in normal adult tissues, embryos and tumors. *Mol Cell Biol* 1985; **5**: 2851–5.
6. Levine AJ, Momand J, Finlay CA. The p53 tumour suppressor gene. *Nature* 1991; **351**: 453–6.
7. van den Berg FM, Tigges AJ, Schipper MEI *et al.* Expression of the nuclear oncogene p53 in colon tumours. *J Pathol* 1989; **157**: 193–9.
8. Scott N, Sagar P, Stewart J *et al.* p53 in colorectal cancer: clinicopathological correlation and prognostic significance. *Br J Cancer* 1991; **63**: 317–19.
9. Sun X-F, Cartensen JM, Zhang H *et al.* Prognostic significance of cytoplasmic p53 oncoprotein in colorectal adenocarcinoma. *Lancet* 1992; **340**: 1369–73.
10. Maddox PH, Jenkins D. 3-Aminopropyltriethoxysilane (APES): a new advance in section adhesion. *J Clin Pathol* 1987; **40**: 56–60.
11. Hsu SM, Raine L. Versatility of biotin labelled lectins and avidin–biotin–peroxidase complex for the localisation of carbohydrate in tissue section. *J Histochem Cytochem* 1982; **30**: 157–61.
12. Graham RC, Karnovsky MJ. The early stages of absorption of injected horseradish peroxidase in the proximal tubule of mouse kidney. Ultrastructural cytochemistry by a new technique. *J Histochem Cytochem* 1966; **14**: 291–302.
13. Riddell RH, Goldman H, Ransohoff DF *et al.* Dysplasia in inflammatory bowel disease: standardised classification with provisional clinical applications. *Hum Pathol* 1983; **14**: 931–68.
14. Crohn BB, Rosenberg H. The sigmoidoscopic picture of chronic ulcerative colitis. *Am J Med Sci* 1925; **170**: 220–3.
15. Lennard-Jones JE, Morson BC, Ritchie JK, Williams CB. Cancer surveillance in ulcerative colitis. Experience over 15 years. *Lancet* 1983; **ii**: 149–52.
16. Myrvold HE, Kock NG, Ahren C. Rectal biopsy and pre-cancer in ulcerative colitis. *Gut* 1974; **15**: 301–4.
17. Nugent F, Haggitt R, Colcher H, Kutteruf G. Malignant potential of chronic ulcerative colitis. *Gastroenterology* 1979; **76**: 1–5.
18. Morson BC. The polyp cancer sequence in the large bowel. *Proc R Soc Med* 1974; **67**: 451–7.
19. Langman MJ. Epidemiology of cancer of the large intestine. *Proc R Soc Med* 1966; **59**: 132–4.
20. Ritchie JK, Hawley P, Lennard-Jones JE. Prognosis of carcinoma in ulcerative colitis. *Q J Med* 1981; **170**: 263–79.
21. Vogelstein B, Fearon ER, Hamilton SR *et al.* Genetic alterations during colorectal tumor development. *N Engl J Med* 1988; **319**: 525–32.
22. Bos JL, Fearon ER, Hamilton SR *et al.* Prevalence of *ras* mutations in human colorectal cancers. *Nature* 1987; **327**: 293–7.
23. Melzer SJ, Mane SM, Wood PK *et al.* Activation of c-Ki-*ras* in human gastrointestinal dysplasias determined by direct sequencing of polymerase chain reaction products. *Cancer Res* 1990; **50**: 3627–30.
24. Burmer GC, Levine DS, Kulander BG *et al.* c-Ki-*ras* mutations in chronic ulcerative colitis and sporadic colon carcinoma. *Gastroenterology* 1990; **99**: 416–20.
25. Finlay CA, Hinds PW, Tan TH, Eliyahu D, Oren M, Levine AJ. Activating mutations for transformation by p53 produce a gene product that forms an hsc70–p53 complex with an altered half-life. *Mol Cell Biol* 1988; **8**: 531–9.
26. Lane DP, Crawford LV. T antigen is bound to a host protein in SV40-transformed cells. *Nature* 1979; **278**: 261–3.
27. Burmer GC, Crispin DA, Venkateswara RK *et al.* Frequent loss of a p53 allele in carcinomas and their precursors in ulcerative colitis. *Cancer Commun* 1991; **3**: 167–72.
28. Greenwald BD, Harpez N, Yin J *et al.* Loss of heterozygosity affecting the p53, *Rb* and *mcc/app* tumour suppressor gene loci in dysplastic and cancerous ulcerative colitis. *Cancer Res* 1992; **52**: 741–5.
29. Burmer GC, Rabinovitch PS, Haggitt RC *et al.* Neoplastic progression in ulcerative colitis: histology, DNA content and loss of a p53 allele. *Gastroenterology* 1992; **103**: 1602–10.

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New technique to measure mucosal metabolism and its use to map substrate utilization in the healthy human large bowel

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A new method of assessing substrate utilization in gastrointestinal mucosal specimens is described. Small human endoscopic biopsy specimens with wet weights ranging between 1·4 and 12·2 mg were used to quantify the oxidation of three metabolic substrates, glucose, glutamine and butyrate, through to carbon dioxide over a 2-h period. The technique proved to be reproducible and capable of distinguishing variations in mucosal metabolism between individuals ($P < 0{\cdot}0001$ for each substrate). Results were similar to those obtained previously using human and rat colonocytes. To characterize the metabolism of the healthy large bowel, specimens were obtained from five regions in 15 patients who had a normal colonoscopic examination. The results show that butyrate is the preferred fuel source of large bowel mucosa, followed by glutamine, then glucose ($P < 0{\cdot}01$). There was no significant regional variation in utilization of the three substrates between the five regions; with respect to glutamine, this is contrary to previous findings.

There has recently been considerable clinical interest in defining the metabolic activity of the gastrointestinal mucosa[1–3]. This is due to an increasing awareness of the importance of mucosal energy metabolism in a variety of large bowel diseases[4]. For example, a lack of luminal butyrate has been implicated as a cause of diversion colitis[5] and a failure to metabolize butyrate has been suggested as a cause of ulcerative colitis[6]. This has led to therapeutic manoeuvres such as the use of butyrate and glutamine enemas to treat these conditions[7–9].

The paucity of information on this subject results, in part, from the difficulties of obtaining metabolic data on human intestinal mucosa. Previous biochemical investigations of gastrointestinal substrate utilization have been hampered by the need for large tissue specimens, which can be obtained only at operation. Hence, it has not been possible to follow the course of a disease or any effects that treatment may have on mucosal metabolism. This has led to the extrapolation of findings from animal experiments, and the results have suggested similarities between the metabolic role of the rumen and the human colon[10–15]; however, there are few confirmatory data. These studies have used a variety of techniques such as mucosal scrapings[16], everted mucosal sacs[17], apical membrane vesicles[18], isolated colonic crypts[19], organ perfusion[20], epithelial (colonocyte) isolation[21] and mucosal strips[14].

As a response to these problems, a technique capable of assessing the oxidation of metabolic fuel sources in small endoscopic biopsy specimens has been devised. The validation of this technique and the results of an investigation of regional variation in the healthy large bowel are described.

The respiratory fuels necessary to maintain cellular function and turnover in intestinal mucosa can be derived from either the intestinal lumen or the circulation. In the small bowel the preferred fuel substrate is glutamine[22]. In the colonic lumen the major available fuels are the short-chain fatty acids acetate, propionate and butyrate, which are produced by anaerobic fermentation of insoluble polysaccharides by bacteria[23]. Of these, butyrate appears to be the major energy source for colonic mucosa[24]. Thus, glucose, glutamine and butyrate were chosen as suitable fuel sources for this investigation.

Patients and methods

All materials were of analytical or equivalent grade. Radioisotopes were obtained from Amersham International (Little Chalfont, UK) and New England Nuclear Du Pont (Dreiech, Germany).

Determination of metabolic activity

The metabolic capability of each biopsy specimen was determined by measuring the ability of the sample to oxidize $[^{14}\mathrm{C}]$glucose, glutamine or butyrate to carbon dioxide over a 2-h incubation. Biopsies were transported to the laboratory in normal saline at 0°C and assayed within 1 h. They were blotted dry, weighed (wet weight data not shown) and placed in a 20-ml MacCartney bottle (*Figure 1*) that contained 2 ml sterile RPMI 1640 cell culture medium (Gibco, Paisley, UK) supplemented with 5 mmol/l L-glutamine and 5 mmol/l sodium butyrate; 11·1 mmol/l glucose was already present. The pH was readjusted to 7·4 by titrating with 1 mol/l sodium hydroxide.

To assess the wet:dry weight ratio for colonic mucosa, five biopsies

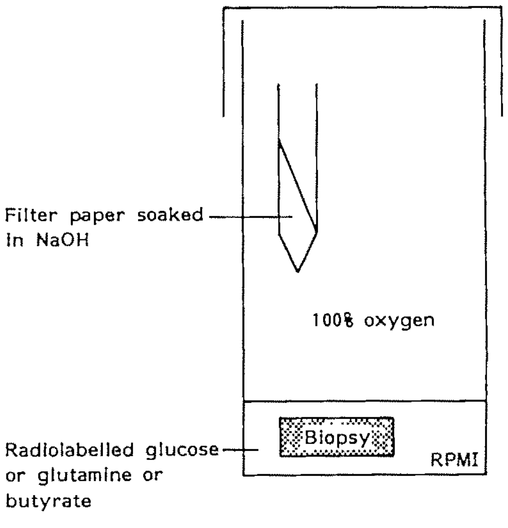
Filter paper soaked in NaOH
100% oxygen
Biopsy
RPMI
Radiolabelled glucose or glutamine or butyrate

Figure 1 *Diagrammatic representation of the assay method*

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from two patients were weighed and dried in an oven at 60°C for 24 h before reweighing. The mean weight reduction was 82 (range 78–85) per cent.

To trace the conversion of the metabolites to carbon dioxide, either 148 KBq D-[U-^{14}C]glucose (Amersham), 37 KBq L-[U-^{14}C]glutamine (Amersham) or 3·7 KBq [1-^{14}C]sodium butyrate (New England Nuclear) was added to each incubation bottle. A 2 × 1 cm glass filter paper (size 10; Whatman, Maidstone, UK) soaked in 120 μl 1 mol/l sodium hydroxide was placed in an Eppendorf (Hamburg, Germany) reaction tube and suspended in the MacCartney bottle. The bottle was sealed with a gas-tight Subaseal (Gallenkamp, Loughborough, UK) before the air was displaced by gassing with 100 per cent oxygen through the seal for 30 s.

After 2 h in a shaking water-bath at 37°C, 0·5 ml 1 mol/l sulphuric acid was injected through the rubber stopper to terminate the incubation and displace the dissolved carbon dioxide from solution. This was absorbed by the sodium hydroxide on the filter paper. The filter paper was removed 30 min later and the trapped radioactivity determined by liquid scintillation counting in 4 ml Optimase Hiphase II Scintillant (Packard Instruments, Groningen, The Netherlands) using a Beckman LS200 scintillation counter (Beckman Instruments, High Wycombe, UK).

The biopsy specimens were then recovered and frozen at −70°C until the protein estimation was performed by the method of Lowry *et al.*[25] after homogenization for 1 min in 1 ml phosphate-buffered saline with 0·1 per cent sodium dodecylsulphate using a polytron blender (Kinematica, Luzem, Switzerland). This allowed the final metabolic fluxes to be expressed as picomoles per microgram protein per hour. The presence of 1 mol/l sulphuric acid did not affect the assay: identical results were obtained when it was performed on known concentrations of acid-treated and non-acid-treated bovine serum albumin (data not shown).

Basal radioactivity resulting from the action of the acid on radiolabelled substrate was determined by incubating medium without added biopsy samples, but with the radiolabelled substrate. These values were subtracted from those obtained in the presence of tissue in each case.

Reproducibility

It is not possible to assess the reproducibility of this assay because each biopsy specimen can be used once only. However, this difficulty can be overcome by taking biopsies from immediately adjacent areas of mucosa and assuming that the metabolic capability is the same. Thus, in four patients undergoing surgical resection of the colon, six mucosal biopsies were taken from adjacent regions of normal-looking mucosa, at least 10 cm from any pathological lesion. This was performed for each fuel substrate and the metabolic flux to carbon dioxide assessed.

Tissue viability

Groups of three adjacent mucosal biopsies were taken from a resection specimen in two patients and incubated for times varying from 30 min to 5 h with L-[U-^{14}C]glutamine. Three assays were performed at each time point and the amount of glutamine oxidized calculated.

Microbiology

To assess the number of bacteria being introduced into the reaction tube by the biopsy, homogenates of large bowel mucosa were cultured. Between 0·5 and 1 g normal-looking mucosa was dissected from the bowel of a surgically resected piece of colon, blotted dry and weighed before being ground in a sterile glass homogenizer in 5 ml normal saline. Serial dilutions of the homogenate to 10^{-8} were plated on to blood agar culture plates. These were incubated aerobically and anaerobically for up to 4 days before the number of colony-forming units (c.f.u.) was counted.

The effect of bacterial contamination from the MacCartney bottle or rubber stopper was investigated by comparing the basal counts of tubes and stoppers that had or had not been sterilized.

Assessment of the capability of sodium hydroxide to capture carbon dioxide

To establish whether sodium hydroxide was present in sufficient concentration to absorb the carbon dioxide generated, suspensions of four common gut organisms (*Enterobacter cloacae, Escherichia coli, Enterococcus faecalis, Bacteroides*) were added in 0·25-ml aliquots to RPMI medium instead of the biopsy material so as to oxidize large quantities of the fuel substrate. This was performed three times for each fuel source. Subsequent culture of the bacterial suspensions showed that 1·55 × 10^{9} c.f.u. had been added to each reaction bottle.

Assessment of regional variation of mucosal metabolism in normal large bowel

Colonoscopic biopsy samples were obtained from 11 women (median age 44 (range 26–78) years) and four men (median age 64 (range 61–68) years) with apparently normal colonic mucosa. All the patients had followed a standard bowel preparation regimen using Picolax (sodium picosulphate and magnesium citrate; Ferring Pharmaceuticals, Feltham, UK). Triplicate biopsies were taken from each of five sites of the large bowel: ascending colon (ileocaecal valve to hepatic flexure), transverse colon (hepatic to splenic flexure), descending colon (splenic to sigmoid flexure), sigmoid colon (sigmoid flexure to proximal rectal valve) and rectum.

Ethics

This study was approved by the Tower Hamlets District Ethical Committee and full informed consent obtained from each patient before biopsies were taken.

Statistical analysis

To assess the sample variation, the coefficient of variance (c.v.) and one-way *F* test (analysis of variance: ANOVA) were used. No assumptions were made about the distribution of the data, so the non-parametric Mann–Whitney *U* and Kruskal–Wallis *H* tests were used to assess statistical significance. Confidence Interval Analysis software (British Medical Association, London, UK) was used to calculate confidence intervals, using the Wilcoxon method.

Calculations

The efficiency of the scintillation counter was established by using known concentrations of ^{14}C, so that counts per minute could be converted to disintegrations per minute. The specific activity of each fuel substrate was calculated from the radioactive concentration given by the manufacturer's data sheet, allowing for the dilution that occurred when the substrate was added to the cell culture medium. The quantity of fuel oxidized to carbon dioxide was equal to the number of disintegrations per second divided by the specific activity.

Results

Reproducibility

The intersample variation from four experiments using each substrate is shown in *Table 1*. A one-tailed *F* test (ANOVA) on variance ratios of the results from the biopsies of the 15 patients studied shows that this assay can distinguish variations in the mucosal metabolism of these fuel substrates between individuals (*Table 1*).

Tissue viability

Glutamine oxidation occurred at a linear rate ($r = 0·99$, $P < 0·001$; $r = 0·97$, $P = 0·006$) over 5 h (*Figure 2*) for the two patients studied.

Microbiology

In the three experiments there were, respectively, 50, 0 and 3 c.f.u. per 10 mg wet weight of tissue that grew aerobically. The anaerobic culture yielded 980, 5800 and 0 c.f.u. per 10 mg.

There was no significant difference between the basal counts

Table 1 *Intersample coefficient of variance calculated from four experiments, each comprising six biopsies*

	Intersample coefficient of variance (%)*	*F* for interpatient variation†	
Glucose	24 (15–26)	5·25‡	v_1 13 v_2 49
Glutamine	23 (7–37)	22·97‡	v_1 14 v_2 53
Butyrate	21 (17–26)	5·26‡	v_1 13 v_2 52

*Values are mean (range). †The one-tailed *F* test was performed on the results from the 15 patients studied; v_1 and v_2 are the upper and lower degrees of freedom respectively. ‡$P < 0·0001$

of the bottles and stoppers that were sterilized and those that were not (*Table 2*).

Assessment of the capability of sodium hydroxide to capture carbon dioxide

During the experiment with bacterial cultures, counts obtained were an order of magnitude higher than the highest counts obtained using mucosal tissue. Thus, sodium hydroxide was present in sufficient quantity to absorb the carbon dioxide generated by the biopsies. Bacteria oxidized glucose at a rate of $8·6 \times 10^{-4}$ pmol per c.f.u. per h, glutamine at $2·3 \times 10^{-4}$ pmol per c.f.u. per h and butyrate at $8·9 \times 10^{-6}$ pmol per c.f.u. per h.

Assessment of regional variation of mucosal metabolism in normal large bowel

While there was a degree of variation between the median colonic utilization of the substrates between individuals (*Table 3*), there was no significant variation in substrate oxidation between any of the sites of the large bowel (H = 3·28, 3·04 and 0·97 for glucose, glutamine and butyrate, respectively; P not significant).

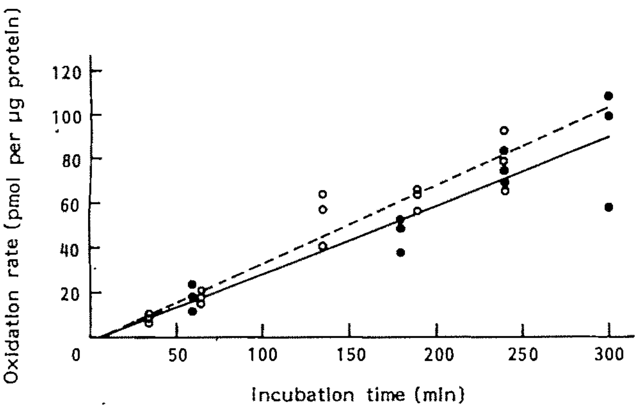

Figure 2 *Rate of glutamine oxidation in colonic mucosa from two patients. Three biopsies were assayed at each time point and the linear regression lines plotted (——, o: r = 0·989, P < 0·001; ——, •: r = 0·969, P = 0·006). The x axis intercept is not significantly different from the origin*

Table 2 *Effect of sterilizing the MacCartney bottles and stoppers on the basal count for each substrate*

	Glucose*		Glutamine*		Butyrate*	
Experiment no.	Non-sterile	Sterile	Non-sterile	Sterile	Non-sterile	Sterile
1	253	354	78	44	245	175
2	357	501	56	60	136	167
3	352	428	36	59	187	198

Values are expressed as colony-forming units. *P not significant (non-sterile *versus* sterile; F values were 3·88, 0·03 and 0·08 for glucose, glutamine and butyrate respectively)

There being no significant regional variation in substrate oxidation, a median value was calculated for each patient, and from this a median for the population investigated was obtained (*Figure 3*). This showed that butyrate is the preferred fuel source, followed by glutamine, then glucose ($P < 0·01$).

Only one attempt was made to obtain each sample so as to minimize the duration of colonoscopy; hence values were not obtained for all the colonic regions. Rarely (<2 per cent) results were not obtained because of contamination of the filter paper with neat isotope or failure to retrieve the specimen for protein estimation.

Discussion

Studies on human mucosal metabolism are rare. Roediger and Truelove[21] harvested large bowel epithelial cells (colonocytes) from surgical resection specimens, so could not study the sequential changes that occur during disease exacerbation and remission or the effects of treatment.

In the present study a technique has been reported that enables quantitative estimation, under controlled conditions, of fuel substrate oxidation to carbon dioxide in mucosal biopsy specimens. The technique is simple to use and requires only small pieces of tissue of 1·4–12·2 mg wet weight. This allows a large number of experiments to be performed, which is particularly valuable for metabolic studies. The intersample c.v.

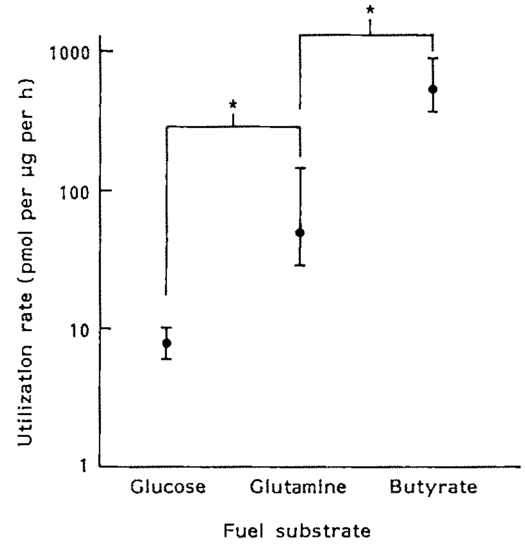

Figure 3 *Rate of utilization of glucose, glutamine and butyrate in normal colonic mucosa. Values are median (95 per cent confidence interval). *P < 0·01 (Mann–Whitney* U *test)*

Table 3 *Regional tissue oxidation of glucose, glutamine and butyrate to carbon dioxide*

	Glucose		Glutamine		Butyrate	
	Oxidation rate*	No. of patients	Oxidation rate*	No. of patients	Oxidation rate*	No. of patients
Ascending colon	7·1 (5·7–11·9)	7	63 (38–442)	8	446 (270–1442)	7
Transverse colon	6·5 (4·6–18·0)	9	76 (36–402)	10	508 (266–1233)	10
Descending colon	9·5 (6·2–18·5)	11	84 (22–180)	12	568 (377–4142)	11
Sigmoid colon	9·3 (6·6–17·4)	12	43 (23–98)	14	555 (354–5764)	11
Rectum	9·0 (5·2–22·1)	11	99 (43–213)	11	533 (382–681)	9

*Values are median (95 per cent confidence interval) expressed as pmol carbon dioxide per µg protein per h

Table 4 *Maximum energy yields from fuel substrates*

When fully oxidized:	
1 mol glucose yields	38 mol ATP
1 mol glutamine yields	30 mol ATP
1 mol buyrate yields	25·5 mol ATP
In normal colon:	
Glucose yields	0·3 nmol ATP per μg protein per h
Glutamine yields	1·4 nmol ATP per μg protein per h
Butyrate yields	13·3 nmol ATP per μg protein per h

ATP, adenosine 5′-triphosphate

is large but similar values have been obtained in other metabolic work such as the investigation of bile acid absorption by the ileal mucosa[26]. This may be partly because it is impossible to obtain two metabolically identical pieces of tissue.

The variation in substrate utilization between patients, which is greater than the intersample c.v., may be due to a number of causes. It is of interest that the concentration of butyrate within the colon is dependent on diet[27,28] and that fasting causes a decrease in the oxidation of glucose, glutamine and butyrate in rat colonocytes[29]. Therefore, it is most likely that variation between individuals is a normal phenomenon that may be ascribed to genetic variation and, perhaps, to long-standing differences in diet.

It has been shown that there are fewer than 6000 bacterial c.f.u. in a 10-mg (approximately 500 μg protein) biopsy specimen. If it is assumed that all 6000 c.f.u. are capable of oxidizing the fuel sources despite the aerobic environment, then the rate of consumption of glucose would be 5·1 pmol/h, of glutamine 1·4 pmol/h and of butyrate 0·053 pmol/h. This is only a small fraction of the amount oxidized by the biopsy specimens. Thus, it is highly unlikely that bacteria are responsible for utilizing a significant quantity of substrate.

The biopsies exhibited a linear rate of substrate utilization (*Figure 2*). There is no lag phase in the rate of glutamine oxidation at the start of the incubation period and the tissue remains metabolically active for at least the 2-h incubation.

The findings in this study show that, in the human colon, butyrate is oxidized in greater amounts than glutamine or glucose (*Figure 3*). However, glucose is a six-carbon structure and so contains more energy than the four-carbon butyrate molecule. The maximum energy yields were calculated (*Table 4*) from the median values in *Figure 3*. It can be seen that, of the three energy sources, butyrate is the most important; this confirms earlier evidence obtained from human colonocytes that butyrate is a major energy source for large bowel mucosa[24].

Roediger[24] found that in human colonocytes, in the presence of 10 mmol/l glucose, the flux of [1-^{14}C]butyrate to carbon dioxide was about 1 μmol per min per g dry weight. However, the mean flux from butyrate to carbon dioxide in the present study was 0·5 μmol per min per g wet weight. When this was multiplied by the ratio of dry:wet weight, butyrate flux was approximately 2·5 μmol per min per g dry weight. This is a similar order of magnitude to that found in the colonocyte.

A similar calculation shows that glutamine flux to carbon dioxide in the present study was 83·3 nmol per min per g wet weight and 0·4 μmol per min per g dry weight, similar to the value obtained by Roediger[11] in the rat colonocyte of 1 μmol per min per g dry weight.

Unfortunately, there are no comparable data for the conversion of glucose to carbon dioxide in the colon. However, it has been calculated that only 5–10 per cent of the total glucose utilization in rat colonocytes is accounted for by oxidation to carbon dioxide[10]. If this figure is applied to measurements of total glucose utilization in human colonocytes, which is about 4 μmol per min per g dry weight in the presence of 10 mmol/l butyrate, then the flux to carbon dioxide would be approximately 0·2–0·4 μmol per min per g dry weight. This may be compared with the flux found in the present study of 8·3 nmol per min per g wet weight, equivalent to approximately 0·05 μmol per min per g dry weight.

Thus, the present results are of a similar order of magnitude to those of other workers, even though the techniques are very different and whole mucosa is being studied rather than isolated colonocytes.

This assay may overestimate the consumption of butyrate by the mucosa as only one of the carbon atoms is radiolabelled ([U-^{14}C]sodium butyrate is not commercially available) and the assumption is made that if the 1-^{14}C atom is oxidized the other three will have an equal chance of being oxidized. This is likely as the butyrate molecule is cleaved to form two molecules of acetyl coenzyme A, one of which is radiolabelled.

The present study confirms the finding that there is no difference in conversion of butyrate to carbon dioxide between the ascending and descending colon[24]. However, it would be interesting to investigate the production of ketone bodies at different sites, as it has been shown in the rabbit that ketogenesis decreases from the caecum to rectum as more of the luminal butyrate is oxidized to carbon dioxide. This suggests that the distal colon is more reliant on butyrate than the proximal colon[14]. Animal studies using unlabelled glutamine have shown a decrease in glutamine oxidation on distal progression along the large bowel[30]. The present authors have been unable to confirm this in the human. This may be because one of the [^{14}C]glutamine atoms might enter the Krebs' cycle at a point other than α-ketoglutarate as a result of, for example, transamination. Alternatively, a small change may be masked by the large interpatient variation. However, *in vivo* reliance on luminal glutamine is probably minimal as it would be avidly utilized by the gut flora as an energy and nitrogen source[31].

It is not surprising that glucose oxidation does not exhibit regional variation, as glucose appears to be of only minor importance as a fuel source and would be delivered to the mucosa via the circulation.

The microtechnique for assessing substrate utilization in gastrointestinal mucosa reported in the present paper yields similar results to those found in the study of rat and human colonocytes. Because only small biopsy samples are required, exciting new possibilities are opened up for the study of diseased mucosa. The technique also allows *in vitro* assessment of new therapeutic agents aimed at treating mucosal disease, and could be applied to mucosa from other organs such as the bladder.

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References

1. Latella G, Caprilli R. Metabolism of large bowel mucosa in health and disease. *Int J Colorectal Dis* 1991; **6**: 127–32.
2. Rabassa AA, Rogers A. The role of short chain fatty acid metabolism in colonic disorder. *Am J Gastroenterol* 1992; **87**: 419–23.
3. Roediger WEW. Bacterial short-chain fatty acids and mucosal diseases of the colon. *Br J Surg* 1988; **75**: 346–8.
4. Roediger WEW. Metabolic basis of starvation diarrhoea: implications for treatment. *Lancet* 1986; **i**: 1082–4.
5. Harig JM, Soergel KH, Komorowski RA *et al.* Treatment of diversion colitis with short chain fatty acid irrigation. *N Engl J Med* 1989; **320**: 23–8.
6. Roediger WEW. The colonic epithelium in ulcerative colitis: an energy deficient disease? *Lancet* 1980; **ii**: 712–15.
7. Breuer RI, Buto SK, Christ ML *et al.* Rectal irrigation with short chain fatty acids for distal ulcerative colitis. *Dig Dis Sci* 1991; **36**: 185–7.
8. De Silva HJ, Ireland A, Kettlewell M, Mortensen N, Jewell DP. Short chain fatty acid irrigation in severe pouchitis. *N Engl J Med* 1989; **321**: 1416–17.
9. Guillemot F, Colombel JF, Lecomte M, Romond C, Paris JC, Cordot A. Treatment of diversion colitis by short chain fatty acids. *Dis Colon Rectum* 1991; **34**: 861–4.

10. Ardawi MSM, Newsholme EA. Fuel utilisation in colonocytes of the rat. *Biochem J* 1985; **231**: 713–19.
11. Roediger WEW. Utilisation of nutrients by isolated epithelial cells of the rat colon. *Gastroenterology* 1982; **83**: 424–9.
12. Binder HJ, Metha P. Short chain fatty acids stimulate active sodium and chloride absorption *in vitro* in the rat distal colon. *Gastroenterology* 1989; **96**: 989–96.
13. Sander EG, Warner RG, Harrison HN, Loosli JK. The stimulatory effect of sodium butyrate and sodium propionate on the development of rumen mucosa in the young calf. *J Dairy Sci* 1959; **42**: 1600–5.
14. Henning SJ, Hird FJ. Ketogenesis from butyrate and acetate by the caecum and the colon of rabbits. *Biochem J* 1972; **130**: 785–90.
15. Henning SJ, Hird FJ. Concentrations and metabolism of volatile fatty acids in the fermentative organs of two species of kangaroo and the guinea-pig. *Br J Nutr* 1970; **24**: 145–52.
16. Rosenthall O, Lasnitzki A. Über den Stoffwechsel stationarer und wacksender Gewebe. *Biochemische* 1928; **196**: 340–425.
17. Parson DS, Paterson CR. Fluid and solute transport across rat colonic mucosa. *Quarterly Journal of Experimental Physiology* 1965; **59**: 220–31.
18. Mascolo N, Rajendran VM, Binder HJ. Mechanism of short chain fatty acid uptake by apical membrane vesicles of rat distal colon. *Gastroenterology* 1991; **101**: 331–8.
19. Gibson PR, Van de Pol E, Maxewell LE, Gabriel A, Doe WF. Isolation of colonic crypts that maintain structural and metabolic viability *in vitro. Gastroenterology* 1989; **96**: 283–91.
20. Roediger WEW, Moore A. The effect of short-chain fatty acid on sodium absorption in isolated human colon perfused through the vascular bed. *Dig Dis Sci* 1981; **26**: 100–6.
21. Roediger WEW, Truelove SC. Method of preparing isolated colonic epithelial cells (colonocytes) for metabolic studies. *Gut* 1979; **20**: 484–8.
22. Windmueller HG, Spaeth AE. Identification of ketone bodies and glutamine as the major respiratory fuels *in vivo* for postabsorptive rat small intestine. *J Biol Chem* 1978; **253**: 69–76.
23. Cummings JH. Short chain fatty acids in the human colon. *Gut* 1981; **22**: 763–79.
24. Roediger WEW. Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. *Gut* 1980; **21**: 793–8.
25. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the folin phenol reagent. *J Biol Chem* 1951; **193**: 265–75.
26. Hosie KB, Davie RJ, Panagamuwa B, Grobler S, Keighley MRB, Birch NJ. Ileal mucosal absorption of bile acid in man: validation of a miniature flux chamber technique. *Gut* 1992; **33**: 490–6.
27. Rombeau JL, Kirpke SA. Metabolic and intestinal effects of short chain fatty acids. *JPEN J Parenter Enteral Nutr* 1990; **14**(Suppl 5): 181S–185S.
28. Rasmussen HS, Holtug K, Anderson JR, Krag E, Mortensen PB. The influence of ispaghula husk and lactulose on the *in vivo* and the *in vitro* production capacity of short chain fatty acids in humans. *Scand J Gastroenterol* 1987; **22**: 406–10.
29. Firmansyah A, Penn D, Lebenthal E. Isolated colonocyte metabolism of glucose, glutamine, *n*-butyrate, and β-hydroxybutyrate in malnutrition. *Gastroenterology* 1989; **97**: 622–9.
30. Pinkus LM, Windmueller HG. Phosphate dependent glutaminase of small intestine: localisation and role in intestinal glutamine metabolism. *Arch Biochem Biophys* 1977; **182**: 506–17.
31. Moat AG, Foster JW. *Microbial Physiology*. 2nd ed. New York: Wiley-Interscience, 1988: 270–9.

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Abdominal aortic aneurysm: still missing the message

Over a 7-month period 50 patients presented to the vascular unit with a ruptured or acute symptomatic abdominal aortic aneurysm (AAA). Information regarding the 24 months before acute presentation was obtained from the patient, family doctor and relevant case records to determine whether an asymptomatic aneurysm had previously been diagnosed but the patient not referred to the vascular service, or whether the patient had undergone an examination at which an aneurysm might reasonably have been expected to be diagnosed. Thirteen patients (26 per cent) had previously had an AAA diagnosed but only five had been referred. Thirteen patients (26 per cent) had had a total of 16 inpatient hospital admissions without an asymptomatic aneurysm being diagnosed. Six patients (12 per cent) underwent abdominal examination for an unrelated complaint by the family doctor without an asymptomatic aneurysm being diagnosed. A significant impact on overall mortality from aortic aneurysm may be made by increasing the number of patients undergoing elective aneurysm repair. All doctors should assess aortic diameter in all patients over 50 years of age who undergo abdominal examination for whatever reason. All patients diagnosed as having an asymptomatic AAA should be referred to a vascular surgeon for assessment.

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Rupture of an abdominal aortic aneurysm (AAA) is responsible for 1·7 per cent of all deaths in men aged 64–75 years[1]. The annual incidence of ruptured AAA has increased to 17 per 100000 population[2] and there has been a corresponding increase in both elective and emergency aneurysm surgery[3,4]. Approximately 5·4 per cent of men aged between 55 and 75 years have an asymptomatic AAA[5] and, once dilatation has occurred, the aorta can be expected to continue to expand[6,7]. Rupture can, however, occur while the aneurysm is still small[8]. After rupture more than half the patients will die before reaching hospital[2]; the overall survival rate has been estimated[9] to be as low as 14 per cent. There is a significant difference in operative mortality rate between elective (4·3 per cent) and emergency (36 per cent) aneurysm surgery[3], leading to calls for increased rates of referral of patients with asymptomatic lesions[10,11]. Screening for small AAAs has also been advocated.

The aim of this study was to determine how many patients with acute symptomatic or ruptured AAA had passed through the hands of the medical profession in the 24 months before acute presentation and who, therefore, might have undergone elective surgery if their condition had been diagnosed and they had been referred for early vascular surgical assessment.

Patients and methods

Fifty consecutive patients referred to the regional vascular surgical service with a diagnosis of acute symptomatic or ruptured AAA were entered into the study, including some who did not have an operation for a variety of medical reasons. Information was gathered from the patient, relatives, family doctor and hospital records regarding the 2-year period before the date of acute presentation to determine whether the aneurysm had previously been diagnosed and the patient appropriately referred, or whether the patient had undergone an examination in either hospital or general practice that could reasonably have been expected to discover the lesion while it was still asymptomatic.

The 50 patients were recruited over a 7-month period commencing April 1991. There were 41 men and nine women, an expected male predominance[12]. The mean(s.d.) age was 72(6) (range 63–83) years. The mean(s.d.) maximum transverse diameter of the aneurysm at presentation was 7·6(1·9) cm; only five were $<5·5$ cm. At the time of acute presentation the size was measured directly at operation, if performed, or by ultrasonography or computed tomography.

Results

Thirteen of the 50 patients presented acutely with an aneurysm that had previously been diagnosed; eight of these 13 had never been referred to the vascular service following diagnosis of an asymptomatic AAA. These eight patients presented acutely at a mean(s.d.) of 13(11) months after diagnosis. The method of diagnosis and aneurysm size at diagnosis and presentation are shown in *Table 1*. The other five patients whose aneurysm had previously been diagnosed had already been referred electively to the vascular service. Three had been considered unfit for elective aortic repair, one with a small aneurysm (4·5 cm in diameter) was being followed up by serial ultrasonography at intervals of 6 months, and the last was awaiting elective aneurysm repair.

Thirteen of the remaining 37 patients had had a total of 16 inpatient admissions in the 24 months before acute presentation (*Table 2*). Six of these 13 patients had had a total of eight admissions for ischaemic heart disease or hypertension, six had undergone recent surgery and one had had two admissions with pneumothorax. These patients subsequently presented acutely with the aneurysm at a mean(s.d.) of 15(6) months following inpatient admission.

Of the remaining 24 patients, six had been examined by their family doctor in the 24 months before acute presentation without a diagnosis of asymptomatic aneurysm being made (*Table 3*). This included two patients who subsequently underwent surgery for an inguinal hernia.

It is apparent, therefore, that only 18 (36 per cent) of the 50 patients with an acutely symptomatic or ruptured AAA had had little or no contact with the medical profession in the 24 months before emergency admission to hospital; a further 27 (54 per cent) had either been diagnosed in the asymptomatic state and not referred for assessment or had been examined but not diagnosed. All of these patients were considered to have aneurysms that were easily palpable.

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Table 1 *Patients in whom an asymptomatic aneurysm had been diagnosed but no referral made*

Age (years)	Sex	Method of diagnosis	Reason for investigation	Final diagnosis	Time to presentation (months)	Size at diagnosis (cm)	Size at presentation (cm)
64	M	Ultrasonography	Abdominal pain	Crohn's disease	17	5·5	10
77	M	Abdominal radiography	Abdominal pain	Cholecystitis	5	—	4·8
76	M	Intravenous urography	Abdominal pain	Ureteric colic	24	—	7
81	M	Laparotomy	Sigmoid colectomy	Colonic carcinoma	24	5	8
61	M	Computed tomography	Assessment of lung tumour	—	1	6	6
70	M	Radiography of lumbar spine	Back pain	Sciatica	4	—	7
70	M	Ultrasonography	Abdominal pain	Myeloma	9	4·5	7
80	F	Ultrasonography	Abdominal pain	Diverticular disease	16	5	7

Table 2 *Patients admitted to hospital in the 24 months before acute presentation without an asymptomatic aneurysm being diagnosed*

Age (years)	Sex	Reason for admission	Time to presentation (months)	Size at presentation (cm)
64	M	Myocardial infarction	11	6·2
77	M	Inguinal hernia repair	23	7·0
74	M	Inguinal hernia repair	13	7·5
74	M	Myocardial infarction	10	8
68	M	Myocardial infarction Coronary artery bypass graft	10 1·5	7·5
70	M	Transurethral resection of prostate	20	7
64	M	Hypertension Hypertension	20 24	7
74	M	Pneumothorax Pneumothorax	11 12	8
63	M	Cardiac catheterization	16	8
82	M	Lens implant	10	8
70	M	Fractured hip	18	12
67	M	Myocardial infarction	22	10
75	M	Transurethral resection of prostate	12	8

Table 3 *Patients examined by their family doctor in the 24 months before acute presentation without an asymptomatic aneurysm being diagnosed*

Age (years)	Sex	Reason for examination	Time to presentation (months)	Reason for non-referral	Size at presentation (cm)
77	M	Inguinal hernia	23	Missed	7
74	M	Inguinal hernia	13	Missed	7·5
74	M	Pulsatile abdominal swelling	Examined 3 times within 1 month	Diagnosed as inoperable cancer	8
70	M	Back pain	3	Missed Plain radiograph showed aneurysm but no action taken	10
70	M	Epigastric mass	2	Missed Referred with gastrointestinal malignancy	9
73	M	Dyspepsia	3	Missed	10

Discussion

The overall mortality associated with AAA could be reduced by increasing the proportion of patients undergoing elective as opposed to emergency aneurysm surgery. Screening for asymptomatic aneurysm has been advocated, although the yield of previously unknown aneurysms ≥4 cm in diameter is low (approximately 2 per cent) in patients selected by age and sex alone; most aneurysms found[5,13–15] are <4 cm. Better results are obtained by screening high-risk groups such as patients with hypertension[16] (5·3 per cent), first-degree relatives of patients with aneurysm[17] (3·9 per cent) and claudicants[18]. Attendance rates for screening, when offered, are about 50 per cent[5,14,15,17]. Unfortunately, most published series continue to report a ratio of elective to emergency operation for aneurysm surgery close to 1:1, despite calls for increased rates of referral[10,11,19]. Referral for elective aneurysm surgery is too often thought inappropriate on the grounds of age and there is a poor perception of outcome[16], yet, even in patients over 80 years old, surgery can be successful with careful case selection[20]. The overall incidence of rupture of an untreated asymptomatic aneurysm[21] is approximately 25 per cent per annum, rising to 50 per cent per annum if the lesion is symptomatic. Referral of patients with small aneurysms may also be considered inappropriate, yet 10 per cent of all ruptures occur[22] when the aortic dilatation is <5 cm.

It is likely that a significant number of patients (16 per cent in the present study) present acutely with a previously diagnosed, but unreferred, aneurysm. If all such patients with aneurysm were referred to a vascular surgeon for assessment, and if aortic size were routinely estimated whenever abdominal examination was performed, the number of patients undergoing elective surgery could be increased even without screening programmes.

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References

1. Collin J. The incidence of abdominal aortic aneurysm. *Br J Surg* 1985; **72**: 499.
2. Ingoldby CJH, Wujanto R, Mitchell JE. Impact of vascular surgery on community mortality from ruptured aortic aneurysms. *Br J Surg* 1986; **73**: 551–3.
3. Naylor AR, Webb J, Fowkes FG, Ruckley CV. Trends in abdominal aortic aneurysm surgery in Scotland (1971–1984). *Eur J Vasc Surg* 1988; **2**: 217–21.
4. Drott C, Arfvidsson B, Ortenwall P, Lundholm K. Age-standardized incidence of ruptured aortic aneurysm in a defined Swedish population between 1952 and 1988: mortality rate and results. *Br J Surg* 1992; **79**: 175–9.
5. Collin J, Araujo L, Walton J, Lindsell D. Oxford screening programme for abdominal aortic aneurysm in men aged 65 to 74 years. *Lancet* 1988; **ii**: 613–15.
6. Collin J, Araujo L, Walton J. How fast do very small abdominal aortic aneurysms grow? *Eur J Vasc Surg* 1989; **3**: 15–17.
7. Walsh AK, Briffa N, Nash JR, Callum KG. The natural history of small abdominal aortic aneurysms: an ultrasound study. *Eur J Vasc Surg* 1990; **4**: 459–61.
8. Jenssen BS, Vestersgaard-Andersen T. The natural history of abdominal aortic aneurysm. *Eur J Vasc Surg* 1989; **3**: 135–9.
9. Budd JS, Finch DR, Carter PG. A study of the mortality from ruptured abdominal aortic aneurysms in a district community. *Eur J Vasc Surg* 1989; **3**: 351–4.
10. Allen PIM, Tudway D, Goldman M. Can we improve community mortality from ruptured aortic aneurysm? *Br J Surg* 1987; **74**: 332.
11. Collin J, Murie J, Morris PJ. Two year prospective analysis of the Oxford experience with surgical treatment of abdominal aortic aneurysm. *Surg Gynecol Obstet* 1989; **169**: 527–31.
12. Fievez M. Aneurysms and arterial dissections. In: Camilleri J, Berry CL, Fiessenger J, Bariety J, eds. *Diseases of the Arterial Wall.* London: Butler and Tanner, 1989: 533–46.
13. O'Kelly TJ, Heather BP. General practice-based population screening for abdominal aortic aneurysms: a pilot study. *Br J Surg* 1989; **76**: 479–80.
14. Collin J, Araujo L, Walton J. A community detection programme for abdominal aortic aneurysm. *Angiology* 1990; **41**: 53–8.
15. Collin J, Araujo L, Lindsell D. A community screening programme for abdominal aortic aneurysms. *Eur J Vasc Surg* 1988; **2**: 83–6.
16. Allen PIM, Gourevitch D, McKinley J, Tudway D, Goldman M. Population screening for aortic aneurysms. *Lancet* 1987; **ii**: 736.
17. Webster MW, Ferrell RE, St Jean PL, Majumder PP, Fogel SR, Steed DL. Ultrasound screening of first-degree relatives of patients with abdominal aortic aneurysm. *J Vasc Surg* 1991; **13**: 9–13.
18. Bengtsson H, Ekberg O, Aspelin P, Kallero S, Bergvist D. Ultrasound screening of the abdominal aorta in patients with intermittent claudication. *Eur J Vasc Surg* 1989; **3**: 497–502.
19. Cheatle TR, Grimley RP. Improving elective referral rate for abdominal aortic aneurysm. *Lancet* 1988; **ii**: 111.
20. Robson AK, Currie IC, Poskitt KR, Scott DJ, Baird RN, Horrocks M. Abdominal aortic aneurysm repair in the over eighties. *Br J Surg* 1989; **76**: 1018–20.
21. Szilagyi DE, Elliot JP, Smith RF. Clinical fate of the patients with asymptomatic abdominal aortic aneurysm and unfit for surgical treatment. *Arch Surg* 1972; **104**: 600–6.
22. Darling RC. Ruptured arteriosclerotic abdominal aortic aneurysms. A pathological and clinical study. *Am J Surg* 1970; **119**: 397–401.

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Reoperation for suspected primary hyperparathyroidism

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A retrospective analysis of 93 patients undergoing 128 re-explorations for persistent or recurrent hypercalcaemia is presented. Seventy-six patients (82 per cent) became normocalcaemic after between one and five reoperations. Nine patients had hypercalcaemia caused by sarcoidosis, familial hypocalciuric hypercalcaemia or metastatic disease, and two had parathyroid carcinoma. Fifteen patients (16 per cent) developed permanent hypoparathyroidism requiring vitamin D and/or calcium therapy and nine had permanent recurrent laryngeal nerve paralysis. Undetected adenomas (41 cases) and inadequate resection in hyperplastic disease (28) were the predominant causes of initial failure. Reoperation for persistent or recurrent hyperparathyroidism restored normocalcaemia in the majority of patients. This 'cure' was achieved at the cost of considerable morbidity and a careful risk–benefit analysis of each patient is recommended before performing reoperative parathyroid surgery.

Persistent or recurrent hyperparathyroidism has become a common clinical problem as the number of patients undergoing cervical exploration for parathyroid disease has increased over the past 15–20 years. This retrospective study of a large number of patients with persistent or recurrent hyperparathyroidism attempts to identify the reasons for initial failure and the risk–benefit of reoperative surgery.

Patients and methods

Between 1973 and 1991, 93 patients (72 women and 21 men; median age 63 (range 22–83) years) underwent 128 parathyroid reoperations. Three surgeons performed 123 of the procedures. The median follow-up was 41 months (range 6 months to 16 years). Seventy-six patients had persistent and 17 recurrent hypercalcaemia. (Recurrent disease was defined as hypercalcaemia occurring >6 months after initial surgery.) The median time to relapse was 44 (range 7–108) months. Sixty-six patients had one reoperation, 21 had two, five had three and one had five reoperations.

The initial neck operation was performed by 31 different surgeons with varying degrees of experience in endocrine surgery. In the operation report the surgeon claimed that four parathyroid glands were identified in 29 cases, three in 21, two in 25 and one in 13. In five cases no parathyroid gland was revealed. Frozen-section examination was used in only 45 per cent of the primary operations.

The median serum calcium concentration (normal range 2·20–2·60 mmol/l) before reoperation was 2·80 (range 2·60–3·45) mmol/l. Serum parathyroid hormone (PTH) concentration, measured with several different antibodies, was raised before operation in 62 patients (67 per cent). Selective catheterization of the neck veins with sampling of blood for PTH determination[1] was performed before 119 of the 128 reoperations. A concentration >50 per cent above the mean value of PTH in the large central veins (subclavian, innominate, superior caval) was considered indicative of an overactive parathyroid gland.

Results

The precise indications for parathyroid reoperation were difficult to assess retrospectively from the patient records. High serum calcium levels (>3·0 mmol/l) were noted in 21 patients (23 per cent) and symptoms of severe hypercalcaemia (fatigue, muscle weakness, mental influence and/or renal stone(s)) in 24 (26 per cent).

Venous sampling gave a correct location in only 27 of 119 investigations (23 per cent; *Table 1*).

The results of reoperative surgery are shown in *Table 2*. Forty-one patients had single adenomas, 28 had hyperplastic

Table 1 *Results of selective neck vein catheterization with parathyroid hormone level determination as localizing technique before 119 reoperations for suspected hyperparathyroidism*

	No. of investigations
Inconclusive	67 (56)
True positive	27 (23)
False positive	6 (5)
Clear parathyroid hormone maximum concentration but no diseased gland found at operation	19 (16)

Values in parentheses are percentages

Table 2 *Surgical results in 93 patients with persistent or recurrent hyperparathyroidism*

	Cured	Not cured
First reoperation ($n = 93$)	60*	33
Second reoperation ($n = 27$)	14	13
Third reoperation ($n = 6$)	5	1
Fourth reoperation ($n = 1$)	0	1
Fifth reoperation ($n = 1$)	1	0

*Four of the patients 'cured' by the first reoperation developed recurrent hypercalcaemia after 12, 54, 74 and 150 months. These four patients were reoperated on a second time

Table 3 *Location of 41 parathyroid adenomas missed at the first exploration*

	No. of cases
Normal	20
Thymus (reached from the neck)	9
Mediastinum	6
Carotid sheath	3
Intrathyroid	2
Retro-oesophageal	1

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Table 4 *Number of parathyroid glands identified and removed at first operation in 28 patients with hyperplastic disease*

	No. of cases
No. of glands identified	
4	10
3	10
2	5
1	3
No. of glands resected	
<1	7
1·5–2	11
2·5–3	10

Table 5 *Reasons for failure of primary neck exploration*

	No.
Poor intraoperative localization	35
Inadequate resection in hyperplastic disease (<2·5 glands)	28
Misdiagnosis (sarcoidosis, familial hypocalciuric hypercalcaemia, metastatic disease)	9
Mediastinal localization	6
Double adenomas	5
Adenoma in fifth gland (4 normal glands identified)	3
Macroscopic misdiagnosis (thyroid nodule mistaken for parathyroid adenoma)	2
Parathyroid carcinoma	2

Table 6 *Outcome in 17 hypercalcaemic patients not cured by reoperative parathyroid surgery*

	No.
Misdiagnosed ($n = 9$)	
Sarcoidosis	4
Familial hypocalciuric hypercalcaemia	3
Malignancy	2
Probably hyperparathyroid but not reoperated on ($n = 6$)	
Asymptomatic, slight hypercalcaemia	3
Dead before reconsideration	1
Old age, heart problems	1
Refused repeat operation	1
Parathyroid carcinoma	2

disease and seven were cured despite no abnormal parathyroid gland being removed at reoperation. One patient with hyperplastic disease, cured after a second reoperation, was subsequently shown to have multiple endocrine neoplasia type I syndrome.

The cause of failure was determined in 69 initial operations (*Tables 3* and *4*). Undetected adenomas and inadequate resection in multiglandular disease were the predominant reasons (*Table 5*).

Various types of surgical procedure were used at reoperation but usually only one side, indicated by preoperative PTH sampling, was explored. Parathyroid adenomas were usually removed solely or together with biopsies of one or two normal glands. In hyperplastic disease, removal of parathyroid tissue aimed at preserving half of a gland *in situ* or transplanting it to the sternocleidomastoid muscle. One and a half glands were removed at reoperation in each individual (median value).

Two intrathyroidal parathyroid adenomas were found in 47 resected thyroid specimens (generally subtotal resection of the lower part of one thyroid lobe). Mediastinal exploration was carried out in 15 patients and six parathyroid adenomas were found.

Nine hypercalcaemic patients were not cured by reoperative parathyroid surgery and were subsequently shown to have other conditions (*Table 6*).

Complications

Permanent paralysis of the recurrent laryngeal nerve occurred in nine patients (10 per cent). Bilateral recurrent nerve paralysis was not observed.

Permanent postoperative hypocalcaemia was present in 15 patients (16 per cent: nine with adenomas, six with hyperplastic disease). In 11 of these, hypocalcaemia appeared after the third or fourth neck exploration. All hypoparathyroid patients achieved nomocalcaemia with calcium and/or vitamin D supplementation.

Discussion

Some 82 per cent of the patients in this study had persistent or recurrent hypercalcaemia cured by surgery, which is slightly lower than the rate of 72–100 per cent reported by others$^{2-13}$ (*Table 7*). Complications were not uncommon and the frequencies of nerve damage and permanent hypocalcaemia were five to ten times higher than usually reported after primary

Table 7 *English language reports on results* of reoperative parathyroid surgery including more than 40 reoperations*

Reference	Year	No. of reoperations	Cure rate (%)†	Complication rate (%) Palsy	Complication rate (%) Hypocalcaemia
Wang[2]	1977	112	91	0	3
Edis *et al.*[3]	1978	54	72	2	30
van Vroonhoven and Muller[4]	1978	51	100	4	2
Granberg *et al.*[5]	1982	79	83	—	13
Brennan and Norton[6]	1985	179	90	6	—
Grant *et al.*[7]	1986	157	89	4	14
Kristoffersson *et al.*[8]	1986	45	74	9	6
Bruining *et al.*[9]	1987	89	—	—	—
Cheung *et al.*[10]	1989	83	86	1	10
Katz and Formichella[11]	1989	42	100	—	—
Levin and Clark[12]	1989	89	91	—	—
Rothmund *et al.*[13]	1990	70	96	6	27
Present series	1993	128	82	10	16
Median			90	4	13

*If several studies have been published from the same institution, only the largest was incorporated in this summary. †Defined as elimination of hypercalcaemia exploration. Vocal cord paralysis frequently occurs despite intraoperative visualization of the recurrent laryngeal nerve[14].

This high morbidity rate suggests that not all patients with persistent or recurrent hyperparathyroidism should undergo neck re-exploration[6,15]. In the absence of overt symptoms of hypercalcaemia, patients with slightly to moderately raised levels (serum calcium <2·9 mmol/l) probably fare better without additional surgery. The results from the present study indicate that this conservative policy is particularly appropriate when the initial operation was performed by an experienced endocrine surgeon or when all four glands were identified at the first exploration.

The criteria for selecting hypercalcaemic patients for parathyroid re-exploration are not usually given when presenting the results of surgery[4,8] and may be defined only as patients with previous neck surgery and hypercalcaemia. Such broad inclusion criteria allow great variation in study populations, accounting for the varying cure rates reported in *Table 7*.

In the present study, failure of the first operation was related to the operating surgeon's performance and the pathophysiological disorder of the patient (*Table 5*). The most common reason for failure was poor intraoperative localization of the adenoma. Primary parathyroid surgery should therefore be performed or supervised by an endocrine surgeon familiar with the normal and unusual locations of parathyroid glands in the neck. The second most common reason for failure was inadequate resection in patients with hyperplasia. It has been recommended that between one-half and one normal size gland (50–100 mg) should be left *in situ* or autotransplanted but between one and one and a half remaining glands may result in recurrent or persistent hypercalcaemia.

To minimize the complications in reoperative surgery it is preferable to localize the site of diseased gland(s) before operation. Ultrasonography, computed tomography, thallium–technetium scanning and magnetic resonance imaging have success rates of between 60 and 70 per cent in cases of persistent or recurrent hyperparathyroidism[10,11,16–19]. Selective venous sampling with PTH analysis may be successful in about 80 per cent of cases[20–22]. Intra-arterial digital subtraction angiography has an accuracy of 60–80 per cent[22,23] and similar results have recently been reported for intraoperative ultrasonography[22,24]. Monitoring of urinary adenosine 3′,5′-cyclic monophosphate[25,26] or serum PTH[27] during re-exploration may be helpful. The skills of an experienced endocrine surgeon are the most superior localizing method in this condition[28]. Ultrasonography with percutaneous biopsy and PTH determination of a suspected adenoma can be highly accurate[29].

The main pitfalls in reoperation for persistent or recurrent hyperparathyroidism were outlined by Hellström[30] in 1957. Mediastinal exploration is seldom required[3,4] and should include the anterior and posterior mediastinum[31,32]. A relatively common cause of persistent hypercalcaemia is familial hypocalciuric hypercalcaemia[33,34], which represents an error of diagnosis and should be considered especially if only macroscopically normal parathyroid glands have been identified. Family history and determination of urinary calcium excretion usually allow an accurate diagnosis, although some patients display normal urinary calcium concentrations and slightly increased PTH levels[34].

References

1. Hjern B, Almqvist S, Granberg PO, Lindvall N, Wåsthed B. Preoperative localization of parathyroid tissue by selective neck vein catheterization and radioimmunoassay of parathyroid hormone. *Acta Chirurgica Scandinavica* 1975; **141**: 31–9.
2. Wang CA. Parathyroid re-exploration. A clinical and pathological study of 112 cases. *Ann Surg* 1977; **186**: 140–5.
3. Edis AJ, Sheedy PF II, Beahrs OH, van Heerden JA. Results of reoperation for hyperparathyroidism, with evaluation of preoperative localization studies. *Surgery* 1978; **84**: 384–93.
4. van Vroonhoven TJ, Muller H. Causes of failure in the surgical treatment of primary hyperparathyroidism: lessons from 51 successful reoperations. *Br J Surg* 1978; **65**: 297–300.
5. Granberg PO, Johansson G, Lindvall N *et al.* Reoperation for primary hyperparathyroidism. *Am J Surg* 1982; **143**: 296–300.
6. Brennan MF, Norton JA. Reoperation for persistent and recurrent hyperparathyroidism. *Ann Surg* 1985; **201**: 40–4.
7. Grant CS, van Heerden JA, Charboneau JW, James EM, Reading CC. Clinical management of persistent and/or recurrent primary hyperparathyroidism. *World J Surg* 1986; **10**: 555–65.
8. Kristoffersson A, Boquist L, Järhult J. Persistent hypercalcemia after neck exploration – an analysis of 34 cases. *Urol Res* 1986; **14**: 323–5.
9. Bruining HA, Birkenhäger JC, Ong GL, Lamberts SWJ. Causes of failure in operations for hyperparathyroidism. *Surgery* 1987; **101**: 562–5.
10. Cheung PS, Borgstrom A, Thompson NW. Strategy in reoperative surgery for hyperparathyroidism. *Arch Surg* 1989; **124**: 676–80.
11. Katz AD, Formichella D. Fifty-three reoperations for hyperparathyroidism. *Am J Surg* 1989; **158**: 385–7.
12. Levin K, Clark OH. The reasons for failure in parathyroid operations. *Arch Surg* 1989; **124**: 911–15.
13. Rothmund M, Wagner PK, Seesko H, Zilke A. Lehren aus Re-Operationen bei 55 Patienten mit primären Hyperparathyreoidismus. *Dtsch Med Wschr* 1990; **115**: 1579–85.
14. Patow CA, Norton JA, Brennan MF. Vocal cord paralysis and reoperative parathyroidectomy. *Ann Surg* 1986; **203**: 282–5.
15. Russell CF, Edis AJ, Purnell DC. The reasons for persistent hypercalcaemia after cervical exploration for presumed primary hyperparathyroidism. *Br J Surg* 1983; **70**: 198–201.
16. Levin KE, Gooding AW, Okerlund M *et al.* Localizing studies in patients with persistent or recurrent hyperparathyroidism. *Surgery* 1987; **102**: 917–25.
17. Miller DL, Doppman JL, Shawker TH *et al.* Localization of parathyroid adenomas in patients who have undergone surgery. Part I. Non-invasive imaging methods. *Radiology* 1987; **162**: 133–7.
18. Järhult J, Kristoffersson A, Lundström B, Öberg L. Comparison of ultrasonography and computed tomography in preoperative location of parathyroid adenomas. *Acta Chirurgica Scandinavica* 1985; **151**: 583–7.
19. Clark OH, Okerlund MD, Moss AA *et al.* Localization studies in patients with persistent or recurrent hyperparathyroidism. *Surgery* 1985; **98**: 1083–94.
20. Wells SA, Doppman JL, Bilezikian JP *et al.* Repeated neck exploration in primary hyperparathyroidism: localization of abnormal glands by selective thyroid arteriography, selective venous sampling, and radioimmunoassay. *Surgery* 1973; **74**: 678–86.
21. Granberg PO, Hamberger B, Johansson G *et al.* Selective venous sampling for localization of hyperfunctioning parathyroid glands. *Br J Surg* 1986; **73**: 118–20.
22. Miller DL, Doppman JL, Krudy AG *et al.* Localization of parathyroid adenomas in patients who have undergone surgery. Part II. Invasive procedures. *Radiology* 1987; **162**: 138–41.
23. Lacombe P, Foster D, Dubost C *et al.* Selective intraarterial DSA of the parathyroid glands in patients with hyperparathyroidism after parathyroidectomy. *AJR Am J Roentgenol* 1987; **149**: 479–83.
24. Kern KA, Shawker TH, Doppman JL *et al.* The use of high-resolution ultrasound to locate parathyroid tumors during reoperations for primary hyperparathyroidism. *World J Surg* 1987; **11**: 579–85.
25. Norton JA, Brennan MF, Saxe AW *et al.* Intraoperative urinary cyclic adenosine monophosphate as a guide to successful reoperative parathyroidectomy. *Ann Surg* 1984; **200**: 389–95.
26. Darling GE, Marx SJ, Spiegel AM, Aurbach GD, Norton JA. Prospective analysis of intraoperative and postoperative urinary cyclic adenosine 3′,5′-monophosphate levels to predict outcome of patients undergoing reoperations for primary hyperparathyroidism. *Surgery* 1988; **104**: 1128–36.
27. Irvin GL III, Dembrow VD, Prudhomme DL. Operative monitoring of parathyroid gland hyperfunction. *Am J Surg* 1991; **162**: 299–302.
28. Beazley RM. Reoperative surgery for persistent hyperparathyroidism. *J Natl Med Assoc* 1988; **80**: 537–41.
29. Doppman JL, Krudy AG, Marx SJ *et al.* Aspiration of enlarged parathyroid glands for parathyroid hormone assay. *Radiology* 1983; **148**: 31–5.
30. Hellström J. The causes of unsuccessful or inadequate

parathyroidectomy in hyperparathyroidism. *Acta Chirurgica Scandinavica* 1957; **112**: 79–91.
31. Wang C, Gaz RD, Moncure AC. Mediastinal parathyroid exploration: a clinical and pathological study of 47 cases. *World J Surg* 1986; **10**: 678–95.
32. Dubost CI, Bouteloup PY. Mediastinal exploration by sternotomy in surgery of hyperparathyroidism. 36 cases. *J Chir (Paris)* 1988; **125**: 631–7.
33. Foley TP, Harrison HC, Arnaud CD, Harrison HE. Familial benign hypercalcemia. *J Pediatr* 1972; **81**: 1060–7.
34. Firek AF, Kao PC, Heath H III. Plasma intact parathyroid hormone (PTH) and PTH-related peptide in familial benign hypercalcemia: greater responsiveness to endogenous PTH than in primary hyperparathyroidism. *J Clin Endocrinol Metab* 1991; **72**: 541–6.

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Case report

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Fungating benign ductal adenoma of the breast

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Benign ductal adenomas of the breast may mimic carcinoma and inappropriate mastectomy may be carried out[1]. A patient with this condition is presented, emphasizing the need to obtain a histological report before proceeding to surgery.

Case report

A 75-year-old woman presented with a 4-day history of a discharging right breast lesion. The breast segment had been discoloured for 2 weeks, but there was no history of lump, pain or nipple discharge.

Examination revealed nipple inversion, a 5 × 5 cm bruised area over the lower outer quadrant, with central ulceration and an offensive discharge. No discrete mass was palpable and there was no associated lymphadenopathy. The left breast was normal. The clinical impression was of locally advanced carcinoma and arrangements were made for 'toilet mastectomy'.

Results of fine-needle biopsy were negative for malignant cells. At excision biopsy a cavity containing thick green pus was encountered; this was sterile on subsequent culture. The wound, which was left open, healed in 6 weeks. The lesion had been completely excised and no further surgery was required.

Histopathology

The specimen consisted of an ellipse of skin, 4·5 × 2·3 cm, with a central 0·8-cm defect; a nodule measuring 2·5 × 2 × 2 cm was noted in the underlying tissue. Histological examination revealed skin ulceration. The nodule was arising in and distending a duct (*Figure 1*). It was composed of tubular or glandular structures lined with a double layer of cells, an inner epithelial and an outer myoepithelial layer, surrounded by a dense fibrous stroma. There was no evidence of a papillary growth pattern. Occasional mitoses were noted, as were foci of apocrine metaplasia. The tumour was confined to the duct with no evidence of invasion and showed features of benign adenoma.

Discussion

Solitary duct papillomas of the breast are rare in the elderly[2,3]. They are usually only a few millimetres in size, found close to the nipple in the terminal duct segments, and associated with a serous or serosanguinous discharge. They may infarct or prolapse through the duct orifice[2,3]. Haagensen[2] reported only one abscess which was related to a small papilloma, without skin ulceration.

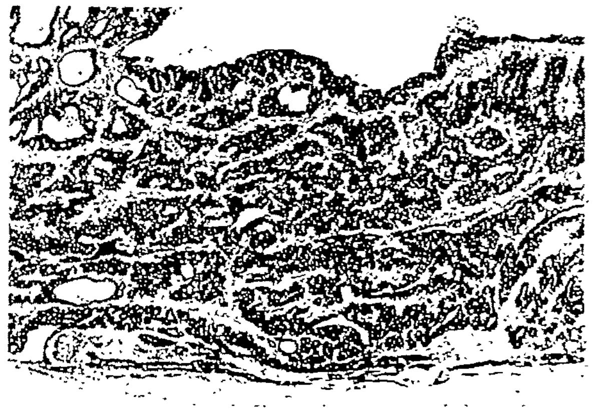

Figure 1 *Low-power photomicrograph showing glandular proliferation filling a large duct. Note the fibrous stroma between glands. (Haematoxylin and eosin stain, original magnification ×30)*

The present lesion was a 'ductal adenoma', which is larger, occurs in an older age group and is more commonly found in the proximal duct segments[1]. The microscopic features typical of a ductal adenoma are of a non-papillary mass composed of tubules lined with epithelial and myoepithelial cells, separated by a moderate amount of connective tissue with a few mitoses[1]. This latter feature, the cellularity, complexity of pattern and apparent capsule invasion can result in confusion with carcinoma, and inappropriate mastectomy may be performed[1,4].

This lesion had the clinical features of a malignant tumour, but cytological analysis revealed only inflammatory cells. Frozen-section biopsy is inadvisable because the histological results may be more confusing and cellular architecture distorted. Open biopsy was performed to include the ulcerated area of skin because a primary disorder of the skin, such as pyoderma gangrenosum or malignant tumour, could not be excluded.

This rare condition helps to emphasize the need for histological confirmation of the diagnosis in breast conditions before proceeding to radical surgery.

References

1. Azzopardi JG, Salm R. Ductal adenoma of the breast: a lesion that can mimic carcinoma. *J Pathol* 1984; **144**: 15–23.
2. Haagensen CD. *Diseases of the Breast*. 3rd ed. Philadelphia, Pennsylvania: WB Saunders, 1986.
3. Hughes LE, Mansel RE, Webster DJT. *Benign Disorders and Diseases of the Breast*. London: Baillière Tindall, 1990.
4. Carney JA, Toorkey BC. Ductal adenoma of the breast with tubular features. *Am J Surg Pathol* 1991; **15**: 722–31.

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Intraoperative assessment of nodal status in the selection of patients with breast cancer for axillary clearance

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Preliminary axillary node sampling with intraoperative reporting of imprint cytology to detect positive nodes was assessed in 50 consecutive patients with T_1 or T_2 breast cancer undergoing axillary clearance, 21 of whom were histologically node positive. A mean of 3·5 (range 1–4) nodes were sampled. Axillary clearance yielded a mean of 11·7 (range 4–32) nodes. Of node-positive patients, sampled nodes detected 18 of 21 on immediate processing, one on subsequent paraffin sections, and failed to detect two (one of ten and one of 17 positive nodes). If the technique had been used during operation to select patients for axillary clearance, 29 of 50 would have avoided the operation, one of two node-positive patients would have required delayed axillary treatment and two of 21 with minimal axillary disease would not have received further axillary treatment or adjuvant therapy. The technique may be useful in reducing the morbidity of breast cancer surgery without increasing the risk of locoregional or distant recurrence.

In patients with operable breast cancer, knowledge of axillary node status is important as a prognostic factor and helps to select women for adjuvant treatment. The involved axilla should be treated to prevent morbidity from uncontrolled locoregional disease. Clinical assessment of axillary node status is, however, unreliable. Veronesi *et al.*[1] reported that 25 per cent of women with clinical stage I disease had histological node involvement, and Edwards *et al.*[2] and Simpson and McIntyre[3] found that palpable nodes could regress after simple mastectomy. Histological examination is at present the only reliable method for assessing axillary node status. Routine axillary clearance would expose a large number of node-negative women to the risk of perioperative and long-term morbidity, for no benefit. Axillary effusions[4] occur in 28–49 per cent of patients and arm swelling[5,6] may occur in 7 per cent. Lymphoedema is uncommon after axillary sampling alone[6] and many accept axillary node sampling as a reliable index of axillary status[7,8]. Others feel that axillary clearance is best[9,10] and argue that radiotherapy following positive node sampling leads to increased morbidity.

Examination of cytological imprints from lymph nodes is useful for intraoperative staging in patients with gastric carcinoma[11] and for postoperative staging in those with breast cancer[12]. The method is quick, sensitive and specific. This study examines whether preliminary axillary node sampling with intraoperative reporting of cytological imprints from the nodes would be a useful method of selecting node-positive women for immediate axillary clearance, thus sparing node-negative women from unnecessary axillary treatment.

Patients and methods

Fifty consecutive women, aged 21–79 years, were studied. Diagnosis was made before operation by clinical examination, fine-needle aspiration biopsy and mammography. Invasive disease was confirmed by frozen section of Tru-Cut (Travenol Laboratories, Deerfield, Illinois, USA) or incision biopsies.

Node sampling was performed through an anterior axillary incision. The pectoral muscles were exposed, cleared to their insertions and retracted forwards. After incision of the anterior axillary fascia, the whole axillary contents were swept from the medial wall and palpated between finger and thumb from apex to axillary tail. Four hard and/or enlarged nodes were sought, dissected without disruption and sent immediately to the histopathology laboratory as sample nodes. The procedure took a maximum of 10 min.

Sample nodes were processed while definitive surgery continued with axillary clearance in all patients. Fat was dissected from the sample nodes which were bisected and the cut surface of one half touched on to a clean slide, which was immediately fixed in formol–acetic alcohol and stained with haematoxylin and eosin. The same half-node was then frozen and sections cut and stained with haematoxylin and eosin before being processed with the other half for paraffin sectioning. Paraffin-embedded material from the sample nodes, the breast and all the axillary clearance nodes was then routinely examined. The number of nodes in the axillary clearance and the total number of positive nodes from sample and clearance were recorded.

All cytological imprints and frozen sections were reassembled, allocated a study number and examined for metastases by two pathologists who were unaware of the nodal status of the patient.

Epithelial cell marker studies were performed on four of the nodes after formalin fixation. The monoclonal antibodies CAM 5.2 (Becton–Dickinson, Cowley, UK)[13] and EMA (Dako, High Wycombe, UK)[14] were applied using an indirect strep–avidin–biotin immunoperoxidase technique. CAM 5.2 stains cytokeratin; EMA stains an epithelial cell surface antigen of molecular weight 265–400 kDa.

Results

A mean of 3·5 (range 1–4) sample nodes per patient and 11·7 (range 4–32) total axillary nodes per patient were studied. It was not always possible to sample four nodes, especially when they were small. In one case only one node was found, but it did contain tumour.

Patient analysis

Twenty-one patients were found to have nodal metastases on examination of the whole axillary contents. Of these, 18 were detected by imprint cytology and frozen section of sample nodes. There were three false-negative results. In two cases, the four sample nodes were negative by all methods, but one of ten and one of 17 positive nodes were found after axillary clearance. In the third case, a tumour deposit was found in the routinely processed half of one of the four sample nodes from a patient with a final total of two of 13 positive nodes.

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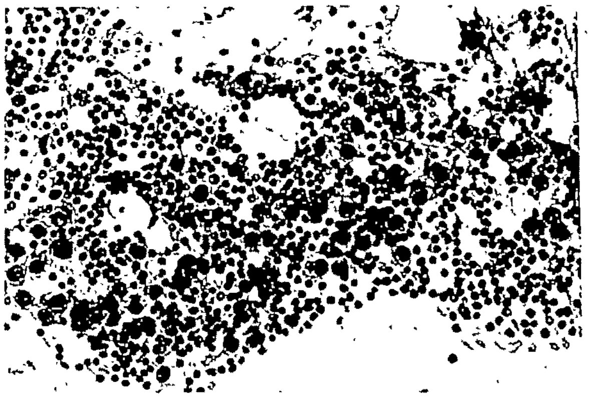

Figure 1 *A positive imprint. Numerous malignant epithelial cells are seen among lymphocytes.* (*Original magnification* ×*400*)

Individual node analysis

The total number of nodes sampled from the 18 patients with positive samples was 61; the individual range was from one to four. Of the 61 nodes, 51 contained tumour on imprint cytology, frozen section or paraffin section. Imprint cytology detected 50 of the 51 nodal metastases (*Figure 1*). It failed to detect tumour in one node. In four nodes it was the only method to identify malignant cells, including the routinely processed haematoxylin and eosin stained section and examination of the remaining half-node. Epithelial cell markers were used on sections of these four nodes. A group of EMA- and CAM 5.2-positive cells was identified in the subcapsular sinus of one node but could not be correlated with cells on the haematoxylin and eosin stained preparation.

Frozen section identified 46 (90 per cent) of the positive nodes. Tumour was not identified in the four nodes found to be positive by imprint cytology alone and there was one further false-negative result.

Discussion

This study shows that a sample of four axillary lymph nodes examined by a rapid tissue-processing technique detects nodal metastases. The sampling method allows reliable identification of positive nodes by the surgeon: 84 per cent of sampled nodes contained tumour in node-positive patients and false-negative results occurred only with minimal axillary disease (one of ten and one of 17 nodes positive).

Imprint cytology failed to identify one of 51 positive nodes. In four nodes it detected tumour cells that could not be shown by any other method, including staining further sections of the nodes with monoclonal antibodies to epithelial cell membranes and cytokeratin. This is consistent with the recognized ability of cytological examination to detect minimal disease[12,15] and the finding of micrometastases on detailed histochemical analysis of axillary nodes previously reported as negative[13,14,16,17]. The significance of such micrometastases is unclear[13,17]. No treatment decisions would have depended on the finding of cytological micrometastases in these patients as other positive sample nodes were present in each case.

Only two women with a single positive node would have been denied adjuvant therapy or further axillary treatment if node sampling and rapid tissue-processing had been the only procedure. The significance of one positive node may not be very great[18].

Operative time for the procedure was limited to 10 min and the nodes were processed during the definitive breast operation. If the results had been used to select patients for axillary clearance, 29 of 50 would have been spared the operation, with an obvious saving in theatre time. During this pilot study laboratory staff formed the subjective impression that good-quality cytological imprints were quicker and easier to prepare than frozen sections of lymph nodes. Cytological examination also detected more positive nodes. Because this pilot study suggests that preliminary node sampling and rapid intraoperative tissue processing will not lead to undertreatment, the technique is now being applied clinically. Node-negative patients undergo no further surgery or radiotherapy to the axilla, while node-positive women proceed to full axillary clearance without axillary radiotherapy. A prospective evaluation of the effect of this policy on perioperative morbidity, duration of hospital stay, long-term arm swelling and shoulder stiffness, and locoregional recurrence is under way.

References

1. Veronesi U, Saccozzi R, Del Vecchio M *et al.* Comparing radical mastectomy with quadrantectomy, axillary dissection and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 1981; **305**: 6–11.
2. Edwards M, Balum M, Magarey C. Regression of axillary lymph nodes in cancer of the breast. *Br J Surg* 1972; **59**: 776–9.
3. Simpson J, McIntyre J. The regression of axillary lymph nodes in relation to prognosis in 'early' breast cancer. *Clin Oncol* 1977; **3**: 125.
4. Inwang R, Hamed H, Chaudary MA, Fentiman IS. A controlled trial of short term *versus* standard axillary drainage after axillary clearance and iridium implant treatment of early breast cancer. *Ann R Coll Surg Engl* 1991; **73**: 326–8.
5. Hoe AL, Iven D, Royle GT, Taylor I. Incidence of arm swelling following axillary clearance for breast cancer. *Br J Surg* 1992; **79**: 261–2.
6. Kissin MW, Querci della Rovere G, Easton D, Westbury G. Risk of lymphoedema following treatment of breast cancer. *Br J Surg* 1986; **73**: 580–4.
7. Steele RJC, Forrest A, Gibson T. The efficacy of lower axillary sampling in obtaining lymph node status in breast cancer: a controlled randomized trial. *Br J Surg* 1985; **72**: 368–9.
8. Kjærgaerd J, Blichert-Toft M, Anderson J *et al.* Probability of false negative nodal staging in conjunction with partial axillary dissection in breast cancer. *Br J Surg* 1985; **72**: 365–7.
9. Kissin MW, Price AB, Thompson EM, Slavin G, Kark AE. The inadequacy of axillary sampling in breast cancer. *Lancet* 1982; **i**: 1210–12.
10. Davies GC, Millis RR, Hayward JL. Assessment of axillary lymph node status. *Ann Surg* 1980; **192**: 148–51.
11. Morris DL. Preoperative lymph node imprint cytology for staging gastric carcinoma. *Br J Surg* 1982; **69**: 282.
12. Quill R, Leahy A, Lawler R, Finney R. Lymph node imprint cytology for the rapid assessment of axillary node metastases in breast cancer. *Br J Surg* 1984; **71**: 454–5.
13. Galea MH, Athanassiou E, Bell J *et al.* Occult regional lymph node metastases from breast carcinoma: immunohistological detection with antibodies CAM 5.2 and NCRC-11. *Br J Pathol* 1991; **165**: 221–8.
14. Wells C, Heryet A, Brochier J, Gatter KC, Mason D. The immunocytochemical detection of axillary micrometastases in breast cancer. *Br J Cancer* 1984; **50**: 193–7.
15. Gentry JF. Pelvic lymph node metastases in prostatic cancer. The value of imprint cytology. *Am J Surg Pathol* 1986; **10**: 718–27.
16. Trojani M, de Mascarel I, Bonichon F, Coindre J, Delsol G. Micrometastases to axillary lymph nodes from carcinoma of breast: detection by immunohistochemistry and prognostic significance. *Br J Cancer* 1987; **55**: 303–6.
17. Sedmak DD, Meineke TA, Knechiges DS, Anderson J. Prognostic significance of cytokeratin-positive breast cancer metastases. *Mod Pathol* 1989; **2**: 516–20.
18. Steele RJC. The axillary node in breast cancer. *J R Coll Surg Edinb* 1983; **28**: 282–91.

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Detection and significance of occult metastases in node-negative breast cancer

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The clinical value of lymph node immunohistochemistry was assessed in 343 consecutive patients with apparently node-negative breast cancer using antimucin monoclonal antibodies BC2, BC3 and 3E1.2. Occult metastases were detected in 41 patients (12 per cent). Although most of these were micrometastatic (<2 mm in diameter), larger or diffuse deposits were found in ten patients. Blind assessment of repeat haematoxylin and eosin stained sections detected metastases in ten of the 41 patients with occult metastases. After a median follow-up of 79 months, patients with occult metastases had a shorter time to disease recurrence ($P < 0{\cdot}05$) *but not to death. After adjustment for other prognostic factors, the presence of occult metastases in two or more nodes was the most significant predictor of both disease recurrence* ($P < 0{\cdot}01$) *and death* ($P < 0{\cdot}01$). *When the ten patients with positive haematoxylin and eosin sections were excluded from the analysis, the presence of occult metastases in two or more nodes was still associated with a reduced disease-free interval* ($P < 0{\cdot}05$) *and survival* ($P < 0{\cdot}05$). *Lymph node immunohistochemistry is a simple technique affording more accurate definition of nodal involvement than conventional methods.*

The most important prognostic indicator in patients with operable breast cancer remains histological lymph node status. Since approximately 15 per cent of patients with negative nodes die within 5 years of diagnosis[1–4], knowledge of nodal status is insufficient to identify all those likely to benefit from adjuvant therapy. The inability of currently available prognostic factors to define high-risk node-negative patients underlies the controversial recommendation that all such women be offered adjuvant therapy[5].

Routine histological practice is to examine haematoxylin and eosin stained sections from one level in each lymph node. Careful review of apparently negative nodes by serial sectioning demonstrates the presence of occult metastases in 9–33 per cent of cases[6–10]. Although the presence of these metastases has generally been held to be insignificant, there have been sporadic reports that nodal micrometastases in the following subgroups are related to poor outcome: those in the upper axilla[11], those associated with T_1 tumours after extended follow-up[12] and those $>1{\cdot}3$ mm in diameter[13]. The recent Ludwig study, analysing 921 patients with negative nodes, demonstrated reduced rates of disease-free survival (58 *versus* 74 per cent) and overall survival (79 *versus* 88 per cent) in those with occult metastases[10]. A drawback of the technique as reported is the large number of sections to be examined: six levels per block from a mean of 12 paraffin blocks per patient. It has been argued that sectioning the node in three equidistant planes yields sufficient information in most cases[7,14].

The superiority of immunohistochemistry over routine haematoxylin and eosin staining in detecting occult metastases in lymph nodes has already been demonstrated[15–19]. Trojani *et al.* are, however, the only workers previously to have assessed the prognostic significance of immunohistochemically detected occult metastases[16,17]. They found the presence of such metastases on the original haematoxylin and eosin sections to be associated with reduced disease-free and overall survival for ductal but not lobular cancers. Over a 12-year period, Trojani *et al.* collected only 122 node-negative patients with ductal cancer[16] but 86 with lobular tumours[17], casting some doubt on the selection of cases.

This study examines the efficacy of a simple immunohistochemical technique in detecting occult nodal metastases in patients with apparently node-negative breast cancer (Union Internacional Contra la Cancrum stage $T_{1-4}\,N_0\,M_0$).

Patients and methods

Patients

A total of 343 consecutive patients with node-negative invasive ductal or lobular carcinoma undergoing surgery between January 1977 and December 1983 were studied. Formalin-fixed paraffin-embedded blocks representing each carcinoma and all processed lymph nodes were retrieved. All patients were originally reported to be histologically node negative and those known to have distant metastases at diagnosis were excluded. Clinicopathological details are given in *Table 1*.

Immunohistochemistry

A mixture of three antimucin murine monoclonal antibodies was used: BC2 (immunoglobulin (Ig) G_1), BC3 (IgM) and 3E1.2 (IgM). The production and use of these antibodies, raised against human mammary carcinoma cells, has been reported previously[20,21]. Immunoperoxidase staining was performed on 4-μm paraffin sections from each carcinoma (positive controls) and all lymph node blocks. The primary antibody mixture was applied for 60 min followed by rabbit antimouse peroxidase conjugate (Dakopatts, Glostrup, Denmark) for 60 min. Sections were developed with diaminobenzidine and counterstained with haematoxylin. Duplicate sections (negative controls) were incubated with an irrelevant IgG antibody (30.6).

Interpretation of immunostaining

Three different patterns of staining of carcinoma were recognized: cytoplasmic, cell membrane and extracellular including juxtaluminal. Primary breast carcinoma sections were graded according to the area (percentage) of cells stained: grade 0, 0 per cent; grade 1, 1–25 per cent; grade 2, 26–50 per cent; grade 3, 51–75 per cent; or grade 4, 76–100 per cent, and average intensity of staining: 0 (negative) up to 4 (intense). The product of the area and intensity grades (immunoscore) was used as a semiquantitative index of staining: score 0 as negative, 1–4 as weak, 6–12 as intermediate and 16 as strong.

Lymph node immunosections were screened by one author (P.J.H.) and all cases of positive or questionable staining reviewed by a second

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Table 1 *Clinicopathological details for patients with and without occult metastases*

	Occult metastases		
	Negative ($n = 302$)	Positive ($n = 41$)	Total ($n = 343$)
Mean (range) age (years)	57·1 (24–85)	54·9 (34–79)	56·9 (24–85)
UICC stage			
pT_1	154	16	170
pT_2	105	19	124
pT_3	5	1	6
pT_{4b}	1	0	1
pT_x	37	5	42
Histological type			
Invasive ductal	285	37	322
Invasive lobular	17	4	21
Bloom and Richardson grade			
1	55	6	61
2	85	18	103
3	138	11	149
Not appropriate	24	6	30
Hormone receptors (cut-off 10 fmol/mg)			
Oestrogen receptor			
Negative	122	13	135
Positive	180	28	208
Progesterone receptor			
Negative	143	11	154
Positive	137	24	161
Not assayed	22	6	28
Surgery			
Total mastectomy	298	41	339
Partial mastectomy	4	0	4
No. of axillary nodes examined			
1–5	61	5	66
6–10	145	20	165
11–15	75	12	87
16–20	18	3	21
21–25	3	1	4
Postoperative adjuvant therapy			
None	259	34	293
Radiotherapy	31	7	38
Chemotherapy	9	0	9
Radiotherapy and chemotherapy	3	0	3

UICC, Union Internacional Contra la Cancrum

(D.M.). Only nodal deposits confirmed on the corresponding haematoxylin and eosin sections were considered positive. Vernier measurements were made of the largest deposit present in each case. The corresponding haematoxylin and eosin sections for all patients with antibody-positive lymph nodes ($n = 41$) and a comparable number with antibody-negative nodes ($n = 41$) were blindly assessed by a third author (R.G.S.) for the presence of metastatic carcinoma.

Histology and hormone receptors

Duplicate haematoxylin and eosin sections from all parent carcinomas were evaluated for histological type and Bloom and Richardson grade[22]. Oestrogen and progesterone receptor levels were measured by a five-point gel filtration radioligand binding assay[23].

Follow-up

Survival and disease-free data were retrieved from the Victorian Cancer Registry, hospital records and attending clinicians and general practitioners by postal questionnaire. Crude survival and disease-free data were obtained for 98 and 75 per cent of patients respectively. The median follow-up was 79 months.

Statistical analysis

Overall survival and disease-free interval were analysed using Kaplan–Meier plots and the log rank test. Factors influencing overall survival and disease relapse were investigated using Cox regression analysis. Correlations were assessed using Kendall's τ.

Results

Immunohistochemical staining

Immunohistochemical staining of the primary breast carcinoma controls was generally strong ($n = 155$; 45 per cent) or intermediate ($n = 141$; 41 per cent). In 45 tumours (13 per cent) staining was weak and in two (1 per cent) negative. Occult metastases were detected immunohistochemically in the lymph nodes of 41 patients (12 per cent). Immunostaining of the 41 corresponding primary tumours was strong in 19 patients (46 per cent), intermediate in 20 (49 per cent), weak in two (5 per cent) and negative in none. The maximum sizes of the occult metastases and number of nodes involved are shown in *Table 2*. Most occult metastases were micrometastatic (<2 mm in diameter) but in ten patients (24 per cent) they were at least 2 mm in size or diffuse. There was a strong correlation between the number of nodes involved with occult metastases and the size of the largest metastasis ($\tau = 0·97$, $P < 0·001$). Although many smaller metastases were emboli situated in the subcapsular sinus, the nodal parenchyma was invaded in 37 of the 41 positive cases.

Of the 41 patients with antibody-positive nodes, metastases were detected by blind review of the corresponding haematoxylin and eosin sections in ten; in four of these only a proportion of the known occult metastases was detected. Of 41 antibody-negative cases no further occult metastases were detected and there was one haematoxylin and eosin false positive. The accuracy of blind haematoxylin and eosin examination did, however, improve with increasing size of the deposits (*Table 2*).

Table 1 gives a breakdown of the parameters studied according to the presence or absence of occult metastases. The groups were broadly similar.

Overall survival and disease-free interval

For the whole study group, the 5-year actuarial mortality rate was 15 per cent (*Table 3*) and disease recurrence rate 17 per cent (*Table 4*). For those with occult metastases, the 5-year actuarial mortality and relapse rates were 13 and 32 per cent respectively. The presence of occult metastases was a significant predictor of disease recurrence (log rank $\chi^2 = 4·90$, 1 d.f., $P < 0·05$) but not of death.

The survival and disease-free rates were compared with the number of nodes involved by occult metastases (*Figures 1* and *2*). The absolute number of nodes involved significantly predicted survival ($\chi^2 = 4·08$, 1 d.f., $P < 0·05$) and disease recurrence ($\chi^2 = 7·06$, 1 d.f., $P < 0·01$). *Figures 1* and *2* show that most difference occurred between patients with none or one and two to four nodes positive ($\chi^2 = 6·56$, 1 d.f., $P < 0·05$ for survival and $\chi^2 = 7·17$, 1 d.f., $P < 0·01$ for recurrence). The final Cox model, therefore, included the same cut-off of none or one *versus* two to four nodes positive for occult metastases.

Table 2 *Morphological features of occult metastases*

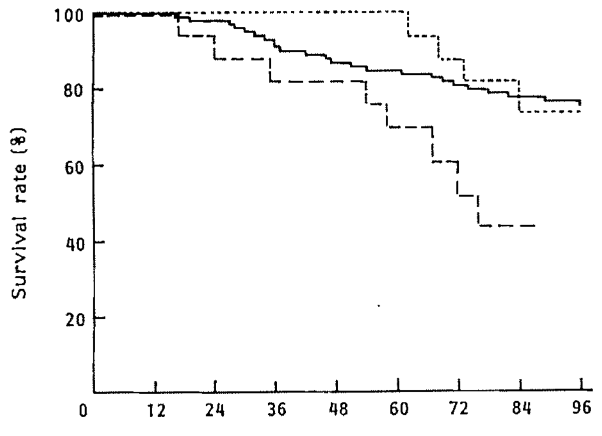
	Haematoxylin and eosin*		
	Negative ($n = 31$)	Positive ($n = 10$)	Total ($n = 41$)
Maximum size of occult metastases (mm)			
<0·1	10	0	10
0·1–0·9	12	4	16
1·0–1·9	4	1	5
2·0–4·0	1	4	5
Diffuse	4	1	5
No. of nodes with occult metastases			
1	20	3	23
2	6	3	9
3	4	4	8
4	1	0	1

*Groups without (negative) and with (positive) nodal deposits recognized on blind review of haematoxylin and eosin stained sections

Table 3 *Actuarial mortality rate and relative risk of death for 343 women with apparently node-negative breast cancer*

Group	No.	5-year mortality rate (%)	Cox logistic regression: *P* Univariate	Cox logistic regression: *P* Multivariate	Cox logistic regression: Relative risk (95% c.i.)*
All	343	15			
Occult metastases					
Negative	302	15	n.s.	n.s.	
Positive	41	13			
H & E positive	10	23			
H & E negative	31	10			
No. of nodes with occult metastases					
0	302	15	<0·05	<0·01	1·00
1	23	0			
2–4	18	30			3·54 (1·68–7·44)
Maximum size of occult metastases (mm)					
<2	31	14	n.s.	n.s.	
≥2	5	25			
Diffuse	5	0			
Age (years)					
<60	185	13	<0·05	<0·05	1·00
60–69	97	15			1·37 (1·03–1·83)
≥70	61	21			1·89 (1·06–3·35)
Tumour size (mm)†					
≤20	170	14	n.s.	n.s.	
>20	131	17			
Histology					
Ductal	322	16	n.s.	n.s.	
Lobular	21	6			
Bloom and Richardson grade					
1	61	9	<0·05	<0·05	1·00
2	103	11			
3	149	21			2·09 (1·29–3·40)
Hormone receptors (cut-off 10 fmol/mg)					
Oestrogen receptor					
Negative	135	18	n.s.	n.s.	
Positive	208	13			
Progesterone receptor					
Negative	154	19	n.s.	n.s.	
Positive	161	10			

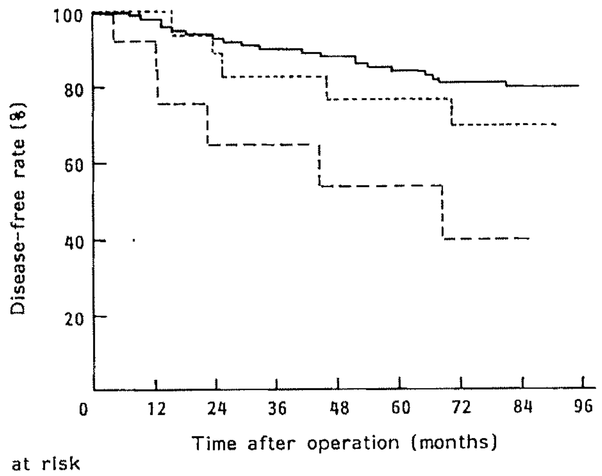
H & E, haematoxylin and eosin; n.s., not significant; c.i., confidence interval. *Relative to the reference groups; †lesions in 42 of the 343 patients were stage pT_x



No. at risk

	0	12	24	36	48	60	72	84	96
No nodes	302	289	279	256	233	214	158	100	66
1 node	23	22	22	22	20	19	14	10	6
≥2 nodes	18	18	16	14	13	11	7	5	

Figure 1 *Survival rate for patients with occult metastases in none (——), one (-----) and two or more (– – –) nodes*



No. at risk

	0	12	24	36	48	60	72	84	96
No nodes	225	215	193	174	157	136	103	70	46
1 node	18	18	17	15	13	12	9	6	
≥2 nodes	13	12	6	6	5	5	3	3	

Figure 2 *Disease-free rate for patients with occult metastases in none (——), one (-----) and two or more (– – –) nodes*

Table 4 *Actuarial disease recurrence rate and relative risk of recurrence for 343 women with apparently node-negative breast cancer*

Group	No.	5-year recurrence rate (%)	Cox logistic regression		
			P		Relative risk (95% c.i.)*
			Univariate	Multivariate	
All	343	17			
Occult metastases					
Negative	302	16	<0·05	n.s.	
Positive	41	32			
H & E positive	10	53	n.s.		
H & E negative	31	24			
No. of nodes with occult metastases					
0	302	16	<0·01	<0·01	1·00
1	23	23			
2–4	18	46			4·00 (1·67–9·58)
Maximum size of occult metastases (mm)					
<2	31	41	n.s.	n.s.	
≥2	5	25			
Diffuse	5	0			
Age (years)					
<60	185	41	n.s.	n.s.	
60–69	97	18			
≥70	61	27			
Tumour size (mm)†					
≤20	170	13	n.s.	n.s.	
>20	131	21			
Histology					
Ductal	322	18	n.s.	n.s.	
Lobular	21	14			
Bloom and Richardson grade					
1	61	20	n.s.	n.s.	
2	103	15			
3	149	20			
Hormone receptors (cut-off 10 fmol/mg)					
Oestrogen receptor					
Negative	135	15	n.s.	n.s.	
Positive	208	19			
Progesterone receptor					
Negative	154	17	n.s.	n.s.	
Positive	161	15			

H & E, haematoxylin and eosin; n.s., not significant; c.i., confidence interval. *Relative to the reference groups; †lesions in 42 of the 343 patients were stage pT_x

Of all the variables tested (*Tables 3* and *4*), the number of nodes positive for occult metastases best predicted death and disease recurrence. No significant relationship was seen between the size of the largest occult metastasis and survival or disease-free interval.

Other variables that were significant predictors of survival but not disease-free interval were age ($\chi^2 = 4·38$, 1 d.f., $P < 0·05$) and Bloom and Richardson grade ($\chi^2 = 5·54$, 1 d.f., $P < 0·05$). Presence of deposits on haematoxylin and eosin blind review, oestrogen receptor and progesterone receptor status, and tumour size were not significantly associated with outcome.

Cox multivariate analysis (*Table 3*) indicated that age (<60, 60–69, ≥70 years), Bloom and Richardson grade (1 or 2 *versus* 3) and number of nodes with occult metastases (none or one *versus* two to four) were independently associated with overall survival. The best predictor of early death was the presence of occult metastases in two or more nodes. For time to disease relapse (*Table 4*), only the presence of occult metastases in two or more nodes was independently significant.

When the ten patients with positive haematoxylin and eosin results were excluded, univariate survival analysis showed no significant reduction in time to disease relapse or death for those with occult metastases. The presence of occult metastases in two or more nodes was, however, still associated with shortened time to recurrence ($\chi^2 = 4·00$, 1 d.f., $P < 0·05$) and death ($\chi^2 = 6·10$, 1 d.f., $P < 0·05$).

Discussion

The detection of nodal metastases is dependent on several factors: the extent of axillary dissection, the thoroughness with which palpable and visible nodes are sought in the operative specimen, the plane in which the node is sectioned and the number of levels examined, the method of staining and the recognition of malignant cells by the pathologist.

This study demonstrated occult metastases in 12 per cent of patients previously considered and treated as node negative. Although many deposits were moderately large, the ability of the antibody mixture to detect small clumps of metastatic carcinoma and even single cells was striking. Macrophages and other single cells occasionally stained positively but were readily dismissed in conjunction with the haematoxylin and eosin section.

The significance of occult metastases of any size and micrometastases (<2 mm in diameter) in regional lymph nodes is currently uncertain. Data from the present study indicate that the presence of occult metastases in two or more lymph nodes has independent prognostic significance, being associated with an increase in the 5-year mortality rate from 15 to 30 per cent and in the disease recurrence rate from 16 to 46 per cent. Even if patients with deposits seen on haematoxylin and eosin blind review are excluded, the presence of occult metastases in two or more lymph nodes still identifies a group with reduced time to relapse and death, although it is recognized that the number of subjects in this group is small ($n = 11$).

The shortcomings of the present study are recognized. Only nine of 75 deaths occurred in the high-risk group with occult metastases in two or more nodes. One possible explanation is that only a single level of each node was studied. Since step sectioning detects occult metastases in up to 33 per cent of patients with negative nodes[6–10] and immunohistochemistry detects four times as many such metastases as haematoxylin and eosin staining, occult metastases may actually be present in the majority of patients with clinical breast cancer. A combination of immunohistochemistry and serial sectioning of axillary lymph nodes would help evaluate the significance of occult axillary metastases.

A further confounding factor may be the treatment given to the axilla in the present series. Axillary clearance may 'cure' some patients with occult metastases, improving their prognosis to the levels seen in those without metastases.

Although the median follow-up was >6 years, patients with node-negative disease may relapse after many years and prolonged follow-up is required to establish the role of occult metastases in such cases.

The National Surgical Adjuvant Breast and Bowel Project[24] demonstrated a near-linear relationship between the number of axillary nodes containing metastases and prognosis. The present study confirms that this observation can be extrapolated to include occult tumour load in apparently negative nodes. Lymph node status is currently used as a major factor in separating groups of patients in clinical trials; it is important to recognize that any report of node status is inherently dependent on the methodology used. Lymph node immunohistology is a useful adjunct to routine histological techniques.

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References

1. Valagussa P, Bonadonna G, Veronesi U. Patterns of relapse and survival following radical mastectomy. *Cancer* 1978; **41**: 1170–8.
2. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24740 breast cancer cases. *Cancer* 1989; **63**: 181–7.
3. Fisher B, Redmond C, Nikolay V *et al.* A randomized clinical trial evaluating sequential methotrexate and fluorouracil in the treatment of patients with node-negative breast cancer who have estrogen-receptor-negative tumors. *N Engl J Med* 1989; **320**: 473–8.
4. Fisher B, Constantino PHJ, Redmond C *et al.* A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med* 1989; **320**: 479–84.
5. Anon. Treatment alert issued for node-negative breast cancer. *J Natl Cancer Inst* 1988; **80**: 550–1.
6. Fisher ER, Swamidoss S, Lee CH, Rockette H, Redmond C, Fisher B. Detection and significance of occult axillary node metastases in patients with invasive breast cancer. *Cancer* 1978; **42**: 2025–31.
7. Pickren JW. Significance of occult metastases. A study of breast cancer. *Cancer* 1961; **14**: 1266–71.
8. Saphir O, Amromin GD. Obscure axillary lymph-node metastasis in carcinoma of the breast. *Cancer* 1948; **1**: 238–41.
9. Wilkinson EJ, Hause LL, Hoffman RG *et al.* Occult axillary lymph node metastases in invasive breast carcinoma: characteristics of the primary tumour and significance of the metastases. *Pathol Annu* 1982; **17**: 67–90.
10. International (Ludwig) Breast Cancer Study Group. Prognostic importance of occult axillary lymph node micrometastases from breast cancer. *Lancet* 1990; **335**: 1565–8.
11. Huvos AG, Hutter RVP, Berg JW. Significance of axillary macrometastases and micrometastases in mammary cancer. *Ann Surg* 1971; **173**: 44–6.
12. Rosen PP, Saigo PE, Braun DW, Weathers E, Fracchia AA, Kinne DW. Axillary micro- and macrometastases in breast cancer. *Ann Surg* 1981; **194**: 595–91.
13. Fisher ER, Palekar A, Rockette H, Redmond C, Fisher B. Pathological findings from the National Surgical Adjuvant Breast Project (protocol No. 4). V. Significance of axillary nodal micro- and macrometastases. *Cancer* 1978; **42**: 2032–8.
14. Wilkinson EJ, Hause L. Probability in lymph node sectioning. *Cancer* 1974; **33**: 1269–74.
15. Raymond WA, Leong AS-Y. Immunoperoxidase staining in the detection of lymph node metastases in stage 1 breast cancer. *Pathology* 1989; **21**: 11–15.
16. Trojani M, de Mascarel I, Bonichon F, Coindre JM, Delsol G. Micrometastases to axillary lymph nodes from carcinoma of breast: detection by immunohistochemistry and prognostic significance. *Br J Cancer* 1987; **55**: 303–6.
17. Trojani M, de Mascarel I, Coindre JM, Bonichon F. Micrometastases to axillary lymph nodes from invasive lobular carcinoma of breast: detection by immunohistochemistry and prognostic significance. *Br J Cancer* 1987; **56**: 838–9.
18. Wells CA, Heryet J, Brochier J, Gatter KC, Mason DY. The immunocytochemical detection of axillary micrometastases in breast cancer. *Br J Cancer* 1984; **50**: 193–7.
19. Bussolati G, Gugliotta P, Morra I, Pietribiasi F, Berardengo E. The immunohistochemical detection of lymph node metastases from infiltrating lobular carcinoma of the breast. *Br J Cancer* 1986; **54**: 631–6.
20. Stacker SA, Thompson C, Riglar C, McKenzie IFC. A new breast carcinoma antigen defined by a monoclonal antibody. *J Natl Cancer Inst* 1985; **75**: 801–11.
21. Xing P-X, Tjandra JJ, Stacker SA *et al.* Monoclonal antibodies reactive with mucin expressed in breast cancer. *Immunol Cell Biol* 1989; **67**: 183–95.
22. Bloom HJG, Richardson WW. Histological grading and prognosis in breast cancer. A study of 1409 cases of which 359 have been followed for 15 years. *Br J Cancer* 1957; **11**: 359–77.
23. Mercer RJ, Lie TH, Rennie GC, Bennett RC, Morgan FJ. Hormone-receptor assays in breast cancer. *Med J Aust* 1983; **1**: 365–9.
24. Fisher B, Bauer M, Wickerham L, Redmond CK, Fisher ER. Relation of number of positive axillary nodes to the prognosis of patients with primary breast cancer. *Cancer* 1983; **52**: 1551–7.

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Antibiotic prophylaxis is indicated for chest stab wounds requiring closed tube thoracostomy

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To determine the role of antibiotic prophylaxis for stab wounds of the chest requiring intercostal tube drainage, a double-blind study was conducted comparing cefazolin, given to 57 patients at 500 mg every 8 h for 24 h, with placebo, given to 56. Differences were detected in the rate of thoracotomy for sepsis (antibiotic nil versus *placebo 9 per cent,* $P < 0\cdot05$*) and in the frequency of sputa positive for pathogens (12* versus *34 per cent respectively,* $P < 0\cdot05$*), but the incidence of pyrexia, raised white cell count, positive cultures from pleural drainage or intercostal catheter tips and volume of chest drainage was similar. The mean hospital stay and costs consequent on morbidity were greater in patients receiving placebo, supporting the conclusion that antibiotic prophylaxis is indicated.*

The rationale of perioperative antimicrobial prophylaxis is well established from animal studies and clinical trials[1]. In areas such as colorectal surgery the indication is beyond debate, but for traumatic haemothorax or pneumothorax requiring intercostal tube drainage the position is not yet clear. Closed tube thoracostomy is an effective method of pleural drainage in trauma with reported empyema rates of <3 per cent[2]. Previous reports, however, included traumatic and spontaneous pneumothorax[3,4] and did not separate blunt from penetrating trauma[5–7] or gunshot from stab wounds[8]. Consequently there is both support for and opposition to the use of antibiotic prophylaxis against overt infection. Previous experience (unpublished results) indicated a complication rate of >10 per cent, no hospital consensus on antimicrobial prophylaxis being found.

If antibiotic prophylaxis is indicated, the agent should have a spectrum covering the pathogens commonly encountered, principally *Staphylococcus aureus*, *Staph. epidermidis* and occasional enteric Gram-negative organisms[9]. Clindamycin[6] and cefoxitin[5] are reported to be of some benefit, but the most widely used agents in cardiothoracic surgery are the first-generation cephalosporins, with broad spectrum and low toxicity. Cefazolin (Kefzol; Eli Lilly, Isando, South Africa) was selected for the present study because it was rarely used institutionally, relatively cheap and could be administered using an 8-h regimen. A randomized double-blind placebo-controlled study was conducted in patients with stab wounds of the chest requiring drainage of the pleural space, to determine whether a difference in the rate of infective complications could be detected.

Patients and methods

All patients sustaining penetrating chest trauma presenting between August 1989 and December 1990 were eligible. The entry criteria were that the injury was sustained within 24 h of admission and placement of an intercostal tube drain for pneumothorax and/or haemothorax, that there were no associated injuries or conditions requiring antimicrobial or antituberculous therapy, and that there was no allergy to penicillin or cephalosporin. Patients with gunshot wounds of the chest and injuries from blunt trauma were excluded, as were cases requiring immediate thoracotomy, patients with multiple injuries and those <12 years of age.

For eligible patients an intercostal drain was inserted under local anaesthesia in the emergency room; a specimen of drainage fluid, if any, was sent for culture and a blood sample submitted for white cell count (WCC). The volume drained was recorded and the first infusion of the coded trial medication commenced. Thereafter, recordings of temperature and volume of drainage daily were made; specimens of sputum for culture and blood for WCC were taken on the third day. On removal of the drain the tip was also submitted for culture. All analyses were performed in the hospital laboratories using standard procedures; anaerobic cultures were not routinely performed.

Of 258 patients with chest trauma, 145 were excluded (*Table 1*) and 113 randomized to receive either cefazolin 500 mg intravenously every 8 h for 1 day ($n = 57$) or three infusions of placebo ($n = 56$). The saline infusions were identically coloured with vitamins and coded in the pharmacy using full double-blind methodology. There were three protocol violations: two patients (one in each group) were receiving antituberculous therapy and another (placebo group) received penicillin before randomization. These cases were analysed on an intention to treat basis. Comparison of the groups for number of stab wounds, time elapsed from injury to presentation, presence of shock (pulse >100/min and systolic blood pressure <90 mmHg), use of

Table 1 *Exclusions from randomization*

Reason for exclusion	No. of patients
Chest drainage not indicated	
Stab not penetrating	59
Small pneumothorax and/or haemothorax	35
>24 h since injury	12
Blunt trauma	7
Heart stab wound	6
Gunshot wound	4
On or requiring antibiotics	5
Associated abdominal stab wound	4
Died after failed cardiopulmonary resuscitation	2
Not entered (reason unknown)	1
Other	10
Total	145

Table 2 *Comparison of study groups*

	Antibiotic group ($n = 57$)	Placebo group ($n = 56$)
Time elapsed since injury (h)*	5·4(4·4)	5·3(4·5)
Median (range) no. of stab wounds	1 (1–7)	1 (1–19)
Shock	5	8
Smokers	35	35
Under influence of alcohol	44	38
Initial drainage volume (ml)*	188(295)	245(435)
Air leak for >24 h	13	15

*Values are mean(s.d.)

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alcohol or cigarettes, and initial drainage volumes were made and the groups found to be similar in these respects (*Table 2*).

The endpoints of the study were defined as thoracotomy, significant pyrexia (temperature >38°C on two or more occasions during admission), positive culture of a known pathogen (from the intercostal drain fluid or tip, or sputum), or an abnormal WCC ($>11 \times 10^9$/l). Patients were managed by their own medical attendants at all times during the hospital stay and this was not modified by the study. Antibiotics were given subsequently as indicated and drains removed when the chest was clear and the drainage was <100 ml/day in most instances, but no specific policy of rapid removal or clamping was followed. The drain wounds were not specifically studied since the presence of a slight purulent discharge was commonplace, although obvious wound collections were documented. Follow-up was complete for at least 4 weeks in all except two patients, who were transferred uneventfully to other hospitals. Chest radiographs were obtained routinely before and after placement of the drain, and before removal to check expansion of the lung, but were not used as an endpoint of the study because of difficulties in interpretation.

Statistical analysis was made using Student's unpaired t test for parametric data and the Mann–Whitney U test and Fisher's exact test as appropriate. Significance was assessed at $P < 0{\cdot}05$.

Results

Thoracotomy was performed in eight patients, significantly more frequently ($P = 0{\cdot}03$) in the placebo group (*Table 3*). Review of the indications showed that in three cases this was not for a septic complication: two were for evacuation of clotted haemothorax and one for bleeding in the first 24 h. The rate of thoracotomy for sepsis (placebo, five; cefazolin, none) remained significantly different ($P < 0{\cdot}05$). The other indications for thoracotomy (all from the placebo group) were empyema in two patients, and one each with loculated collection secondary to pneumonia, haemothorax growing a pathogen, and empyema and subphrenic collection after a transdiaphragmatic stab wound. There were no deaths, but one additional patient receiving placebo required pericardiotomy for sterile serous pericardial effusion and right heart failure 3 weeks after the stab wound. Sputum cultures from patients receiving the placebo grew significantly more pathogens, 34 *versus* 12 per cent ($P = 0{\cdot}03$); the most common isolates were *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Klebsiella*.

The incidence of pyrexia, volume and duration of chest drainage, WCC and rate of positive cultures of initial drain fluid and tip were similar in both groups. Twenty-six patients were pyrexial by definition and in 17 a cause was clinically evident; pyrexia in the remaining nine resolved with physiotherapy. The WCC was found to be raised in 63 patients (56 per cent) on admission and in 26 (23 per cent) on the third day, but this was not shown to relate to antibiotic prophylaxis and in only 31 per cent of cases was an objective cause found.

Table 3 *Comparison of study endpoints*

	Antibiotic group ($n = 57$)	Placebo group ($n = 56$)
Thoracotomy	1	7†
Thoracotomy for sepsis	0	5†
Pyrexia	10	16
Mean(s.d.) white cell count ($\times 10^9$/l)		
Admission	11·7(3·8)	13·1(4·9)
Day 3	9·3(3·4)	10·5(6·3)
Positive culture*		
Initial drainage	0 (23)	1 (19)
Sputum	4 (34)	12 (35)†
Drain tip	25 (46)	25 (41)
Chest drainage		
Mean(s.d.) volume (ml/day)	127(110)	122(134)
Mean(s.d.) duration (days)	3·5(1·7)	4·1(1·9)‡

*Values in parentheses are number of culture specimens; in many cases no specimen could be obtained. †$P = 0{\cdot}03$ (Fisher's exact test); ‡$P = 0{\cdot}06$ (Student's t test)

Cultures from the initial drain fluid were usually sterile and the tips were usually contaminated (*Table 3*), the most common pathogens being *Staph. epidermidis* (62 per cent), *Staph. aureus* (10 per cent), *Acinetobacter* (8 per cent), *Escherichia coli* (6 per cent) and *Strep. pyogenes* (4 per cent).

Mean hospital stay was shorter for patients receiving cefazolin, 3·9 (median 4 (range 2–12)) *versus* 5·6 (median 4 (range 2–21)) days ($P < 0{\cdot}01$) due mainly to the patients undergoing thoracotomy, for whom the median stay was 13 (range 6–21) days. Air leaks for >24 h occurred in 28 patients, two of whom subsequently underwent thoracotomy. However, air leakage did not correlate with positive culture or pyrexia.

In the 145 patients excluded from the study (*Table 1*), the mortality rate was 3 per cent (deaths from stab wounds to the heart and major vessels); 9 per cent required thoracotomy and 2 per cent developed empyema. There were 94 patients for whom a chest drain was not indicated: in 59 the chest radiograph was normal (three later required a drain and one of these needed thoracotomy) and 35 had minimal haemopneumothorax, none of whom subsequently required drainage.

Discussion

Based on the thoracotomy rate, a significant difference in favour of using prophylactic cefazolin was noted. This difference persists if operations unrelated to sepsis are excluded. The low morbidity rate of pleural drainage for stab wounds of the chest may be one reason why antibiotic prophylaxis has not been so far perceived to be justified. However, when the problem is studied prospectively, the complication rate is often higher than expected. Features of infective morbidity range from pyrexia and leucocytosis through to atelectasis, pneumonia and empyema. However, it is major infections requiring intervention, especially thoracotomy, that are the more serious and costly complications.

WCC did not predict those at risk of complication. The counts were raised on admission compared with day 3 but there was no difference between the groups. Similarly, pyrexia was not discriminatory and was often unassociated with demonstrable infection. Raised temperature was usually investigated by chest radiography, but difficulty in interpretation in the presence of surgical emphysema, dressings, lung collapse and pleural reactions caused radiographic signs to be abandoned as a measure of morbidity during the pilot study.

The sputum of patients receiving cefazolin grew fewer pathogens, which might indicate that the antibiotic sterilized the bronchial secretions, reducing the potential for pleural infection. The duration of prophylaxis was limited to 24 h in view of the unproven value of prolonged therapy, the risk of inducing resistance and the cost of the drug[1]. It was, however, considered that more than a single dose was indicated, although recent work[10] suggests that this might not be so. The spectrum of cefazolin covers all the organisms isolated from the thoracotomy specimens, together with the majority from other bacterial cultures, but other drugs may be equally effective. The cost of the antibiotic infusions was £6·25 per patient, or over £350 for the drug arm of the trial. Assuming five additional thoracotomies with infection, the excess in operation costs alone for these patients would be approximately £7000.

In conclusion, this study shows that antibiotic prophylaxis has a clear advantage in patients requiring an intercostal drain for chest stab wounds. Antibiotic is associated with a lower thoracotomy rate and consequent cost saving, which may be due partly to a reduction in the pathogenicity of the sputum.

References

1. Kaiser AB. Antimicrobial prophylaxis in surgery. *N Engl J Med* 1986; **315**: 1129–38.
2. Millikan JS, Moore EE, Steiner E, Aragon GE, Van Way CW. Complications of tube thoracostomy for acute trauma. *Am J Surg* 1980; **140**: 738–41.

3. LeBlanc KA, Tucker WY. Prophylactic antibiotics and closed tube thoracostomy. *Surg Gynecol Obstet* 1985; **160**: 259–63.
4. Stone HH, Symbas PN, Hooper CA. Cefamandole for prophylaxis against infection in closed tube thoracostomy. *J Trauma* 1981; **21**: 975–7.
5. LoCurto JJ, Tischler CD, Swan KG *et al.* Tube thoracostomy and trauma – antibiotics or not? *J Trauma* 1986; **26**: 1067–72.
6. Grover FL, Richardson JD, Fewel JG *et al.* Prophylactic antibiotics in the treatment of penetrating chest wounds. A prospective double blind study. *J Thorac Cardiovasc Surg* 1977; **74**: 528–36.
7. Mandal AK, Montano J, Thadepalli H. Prophylactic antibiotics and no antibiotics compared in penetrating chest trauma. *J Trauma* 1985; **25**: 639–43.
8. Wells FC, Newsom SWB, Rowlands C. Wound infection in cardiothoracic surgery. *Lancet* 1983; **i**: 1209–10.
9. Brunner RG, Vinsant GO, Alexander RH, Laneve L, Fallon WF. The role of antibiotic therapy in the prevention of empyema in patients with an isolated chest injury (ISS 9–10): a prospective study. *J Trauma* 1990; **30**: 1148–54.
10. Demetriades D, Breckon V, Breckon C *et al.* Antibiotic prophylaxis in penetrating injuries of the chest. *Ann R Coll Surg Engl* 1993 (in press).

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Case report

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Protein C deficiency and rapidly progressing peripheral arterial disease

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Occlusion following vascular reconstruction may be related to technical failure or coagulation disorders when early, or to intimal hyperplasia or progressive atherosclerosis when late. A case is presented of rapid progression after femorodistal bypass with occlusion of vessels in both the operated and non-operated leg caused by protein C deficiency.

Case report

A 71-year-old man presented with intermittent claudication with a march tolerance of 50 m. The man had never smoked and was not diabetic. He had had a right total hip replacement 3 years previously, complicated by right deep vein thrombosis confirmed by venography. Some 4 months before admission he was found to have a benign paraproteinaemia (κ chain, immunoglobulin G 17 g/l, erythrocyte sedimentation rate 8 mm/h) and was treated with melphalan.

The right leg pulses were normal; in the left leg only a femoral pulse was palpable. Transfemoral angiography demonstrated normal common and external iliac arteries but an occluded right internal iliac artery. The mid-portion of the left superficial femoral artery was occluded and the tibioperoneal trunk was stenosed.

A femoroposterior tibial reversed vein bypass was performed with good early results. At 2 weeks the patient presented with critical ischaemia in the same leg. Graft occlusion was confirmed angiographically. Graft thrombectomy was unsuccessful and above-knee amputation was performed. During rehabilitation the patient developed critical ischaemia in the other leg. Further angiography demonstrated that the left common iliac and right superficial femoral arteries, previously patent, were occluded. Echocardiography and aortic ultrasonography results were normal.

Because of this rapid progression, protein S, protein C and antithrombin III levels were measured. Protein S and antithrombin III concentrations were normal but the protein C level was 18 per cent (normal range 70–150 per cent). The patient underwent anticoagulation with heparin, then warfarin. The limb rapidly became ischaemic and required below-knee amputation. He died 2 weeks later from a myocardial infarction.

Discussion

Protein C is a vitamin K-dependent glycoprotein and inhibits coagulation by proteolytic inactivation of factors Va and VIIIa which allow conversion of prothrombin to thrombin. Protein C deficiency may be inherited as an autosomal dominant disease[1]. Such a deficiency is associated with venous thrombosis, both peripherally and in the portal circulation[2], but can produce cerebral[3] and mesenteric[4] arterial occlusion and may account for 5 per cent of unexplained thromboses. Affected individuals have concentrations below 50 per cent of normal.

There is an initial paradoxical increase in thrombotic tendency because of the fall in protein C activity that occurs when warfarin anticoagulation commences; this may cause extensive superficial thrombosis and skin necrosis. The rapid deterioration and fatal myocardial infarction following anticoagulation with warfarin in this patient may have resulted from paradoxical thrombosis related to anticoagulation.

Rapid progression of arterial disease in the absence of known risk factors should lead to a search for specific coagulation disorders. Protein C deficiency, if detected, should be treated by cautious anticoagulation with warfarin[5] and the family screened. Early graft failure is usually presumed to result from technical error or poor patient selection, and a diagnosis of hypercoagulable state made only after exclusion of other factors. Coagulation disorders should be sought in patients presenting with thrombosis in unusual circumstances.

References

1. Griffin JH, Evatt B, Zimmerman TS, Kleiss AJ, Wildeman C. Deficiency of protein C in congenital thrombotic disease. *J Clin Invest* 1981; **68**: 1370–3.
2. Dos Santos JN, De Silva AM, Alexandrino P *et al.* Hereditary protein C deficiency and portal vein thrombosis. *Neth J Med* 1991; **38**: 212–16.
3. Matsushita K, Kuriyama Y, Sawada T, Uchida K. Cerebral infarction associated with protein C deficiency. *Stroke* 1992; **23**: 108–11.
4. Bemelman WA, Butzelaar RM, Khargi K, Keeman JN. Mesenteric venous thrombosis caused by deficiency of physiologic anti-coagulants: report of a case. *Neth J Surg* 1990; **42**: 16–19.
5. Towne JB. Hyperthrombotic states and vascular surgical emergencies. In: Greenhalgh RM, Hollier LH, eds. *Emergency Vascular Surgery*. London: WB Saunders, 1992: 11–36.

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Role of reflux oesophagitis and acid in the development of columnar epithelium in the rat oesophagus

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The role of reflux oesophagitis and acid in the development of oesophageal columnar epithelium was investigated in the rat. Twenty-four animals underwent total gastrectomy and oesophagojejunostomy, inducing reflux of duodenal contents into the oesophagus, and were divided into two groups: an 'acid' group, which drank syrup water with hydrochloric acid (pH 1·8), and a 'non-acid' group, which drank only syrup water (pH 6·5). Four rats were killed at 4, 8 and 12 weeks after surgery. Reflux oesophagitis was found in the lower portion of the oesophagus in all cases. Columnar epithelium was observed in the oesophagus of one rat in the non-acid group at week 8 and of three in the acid group at week 12. These results indicate that the development of columnar epithelium of the oesophagus is preceded by reflux oesophagitis and that acidic conditions may promote this change. Columnar epithelialization may result from metaplasia of squamous epithelium as well as from upward extension of columnar epithelium.

Since Barrett[1] originally described the columnar epithelium lining the lower oesophagus in 1950, the histogenesis of this condition has been disputed. Allison and Johnstone proposed that the columnar-lined oesophagus could be an acquired condition resulting from reflux oesophagitis[2]. In a later report, Barrett stated that it was the result of failure of the embryonic lining of the gullet to achieve normal maturity, suggesting a congenital condition[3].

A number of clinical studies concerned with the aetiology of Barrett's oesophagus have been reported. Most have supported the theory of an acquired condition secondary to reflux oesophagitis[4-10], although some have indicated that Barrett's oesophagus can be acquired in adults and may be congenital in children because of the bimodal age distribution with distinct paediatric and adult peaks[11].

Experimental induction of columnar epithelium in the oesophagus was, however, initially unsuccessful. Hennessy *et al.* created a defect in the oesophagus by removing a strip of mucosa, but failed to produce columnar epithelium[12]. Bremner *et al.*[13] and Gillen and colleagues[14] succeeded in producing columnar epithelium in the canine oesophagus by surgical mucosal excision and creation of a hiatal hernia with high acidity.

The present study was designed to evaluate the role of reflux oesophagitis and acid in the development of columnar epithelium of the oesophagus in a rat model.

Materials and methods

Animals

Inbred male Wistar rats weighing approximately 250 g were used. They had been inbred for >60 years in the Institute of Experimental Gerontology, Basel, Switzerland, and the Institute of Pathology, University of Bonn, Germany. Rats were fed a commercial diet (Oriental Yeast Company, Tokyo, Japan).

Experimental design

Twenty-four rats underwent total gastrectomy with reconstruction by oesophagojejunostomy to induce reflux of duodenal contents containing bile and pancreatic juice directly into the oesophagus (*Figure 1*). Animals were fasted for 24 h before surgery. Operative procedures were carried out after intraperitoneal injection of 25 mg/kg pentobarbitone. During the 2 days after surgery, all rats received 10 ml 5 per cent glucose subcutaneously with 50 mg piperacillin. Drinking water was withheld for 24 h and food for 48 h after surgery; thereafter, animals had free access to food and the liquids described below. After operation, rats were divided into two experimental groups. Animals in group 1 (acid group) were given syrup water with hydrochloric acid (pH 1·8; Department of Pharmaceutical Services, Tokyo University) *ad libitum*. Group 2 (non-acid group) animals received syrup water without hydrochloric acid (pH 6·5) *ad libitum*. There was no difference in the sucrose concentration of the syrup waters (68 mg/ml). Each group was divided into three subgroups of four rats each, which were killed 4, 8 and 12 weeks after surgery. After death, the oesophagus was removed and preserved by formalin fixation, then embedded in paraffin and stained with haematoxylin and eosin or alcian blue-periodic acid-Schiff (PAS) for histological examination.

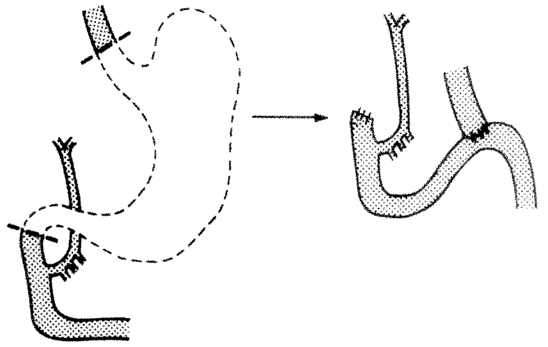

Figure 1 *Surgical procedure after total gastrectomy; oesophagojejunostomy induces reflux of duodenal contents into the oesophagus*

Results

At the end of the experimental period, 11 rats remained alive in group 1 and nine in group 2. Four rats died from pneumonia or peritonitis during the experimental period.

Macroscopic findings

There were no obvious macroscopic differences among the six subgroups. The oesophagus in every rat had a markedly thickened and dilated lower portion, sometimes reaching a

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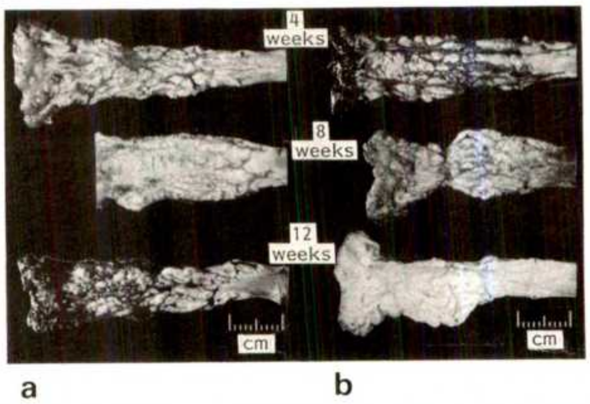

Figure 2 *Macroscopic views of rat oesophagus from* **a** *group 1 and* **b** *group 2. Animals were killed 4, 8 or 12 weeks after surgery; the left side is distal in each specimen*

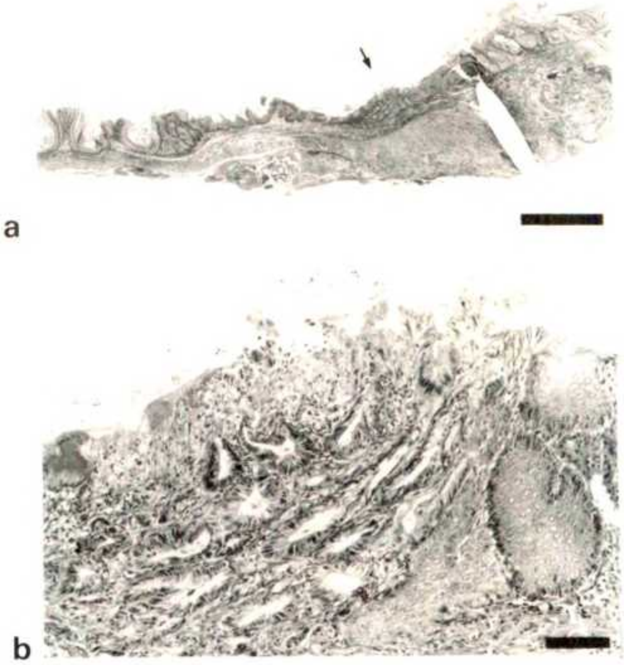

Figure 4 **a** *Island of columnar epithelium (arrow) in the area of reflux oesophagitis.* **b** *Magnification of an island of columnar epithelium. (Haematoxylin and eosin stain, scale bar in* **a** *1 mm, in* **b** *100 μm)*

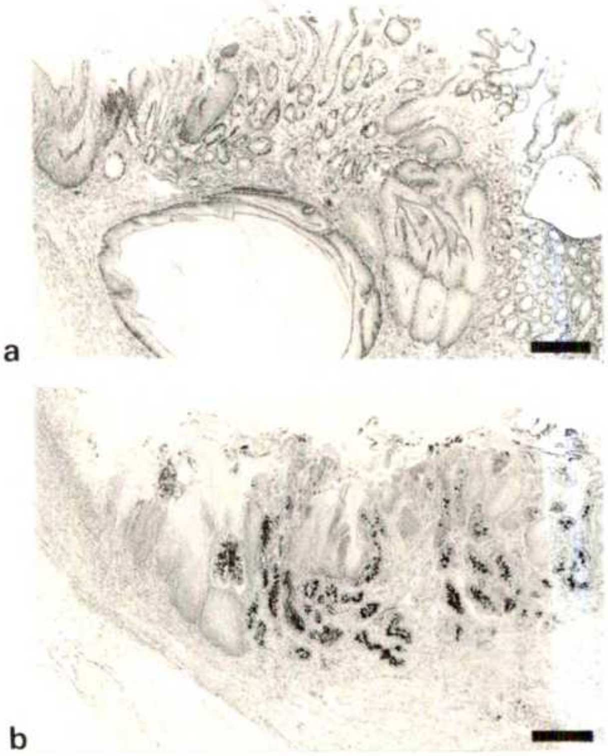

Figure 3 **a** *Columnar epithelium intermingled with squamous epithelium. (Haematoxylin and eosin stain.)* **b** *Cells positive for alcian blue–periodic acid–Schiff staining are intermingled with negatively stained squamous epithelium. (Scale bar 300 μm)*

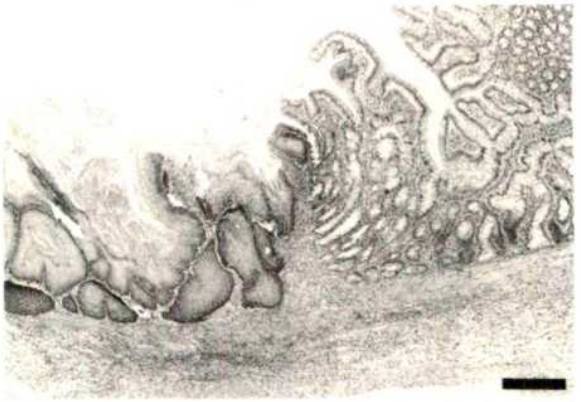

Figure 5 *Magnification of the site of anastomosis in one of the rats that did not develop columnar epithelium of the oesophagus. (Haematoxylin and eosin stain, scale bar 300 μm)*

Table 1 *Incidence of columnar epithelialization of the oesophagus*

Period (weeks)	Group 1	Group 2
4	0 ($n = 4$)	0 ($n = 2$)
8	0 ($n = 4$)	1 ($n = 4$)
12	3 ($n = 3$)	0 ($n = 3$)

diameter more than twice that of normal. The mucosa of the lower oesophagus was grossly irregular with a granular appearance (*Figure 2*). No changes were found in the upper portion of any oesophagus.

Histological findings

The mucosal changes in the lower oesophagus of all rats were confirmed histologically to be those of reflux oesophagitis, which is characterized by basal cell hyperplasia and extension of papillae with ulceration and hyperkeratinization. There was no difference in the severity of reflux oesophagitis between groups 1 and 2.

Table 1 summarizes the incidence of columnar epithelialization of the oesophagus. This is defined as the intermingling of columnar and squamous epithelium (*Figure 3*) or islands of columnar epithelium surrounded by squamous epithelium (*Figure 4*). All the group 1 rats killed 12 weeks after surgery developed columnar epithelium of the oesophagus. One of the three animals had intermingling of columnar and squamous epithelium as well as islands of columnar epithelium; the other two showed only one of these characteristics. One of the group 2 rats killed 8 weeks after surgery developed intermingling of columnar and squamous epithelium. Areas of intermingled columnar and squamous epithelium were adjacent to the site of anastomosis of the oesophagojejunostomy. Islands of columnar epithelium were distant from the site of anastomosis and located in the area of reflux oesophagitis. A definite border between squamous and intestinal epithelium was observed at the site of anastomosis in the other 16 rats (*Figure 5*).

Discussion

Since the work of Ferguson *et al.*[15] many experiments aimed at elucidating the pathogenesis of reflux oesophagitis have been performed. Bile and pancreatic juice have been considered to be crucial factors in the pathogenesis of such oesophagitis in these experiments[16–20]. Therefore, simple oesophagojejunostomy after total gastrectomy, which ensures the regurgitation of bile and pancreatic juice into the oesophagus, was chosen as the experimental model for reflux oesophagitis in the present study.

In an earlier experiment[21], rats underwent total gastrectomy with Roux-en-Y reconstruction, preventing reflux of duodenal contents into the oesophagus, and were killed 17 weeks after surgery. None of the animals undergoing Roux-en-Y reconstruction showed reflux oesophagitis or columnar epithelialization of the oesophagus.

In the present study, all rats killed 4 weeks after surgery in both groups developed reflux oesophagitis but not columnar epithelium of the oesophagus. All the group 1 rats killed 12 weeks after surgery and one of the group 2 animals killed at 8 weeks had columnar epithelialization in the area of reflux oesophagitis. This indicates that columnar epithelium in the oesophagus develops as an acquired lesion secondary to reflux oesophagitis and is promoted by acidic conditions. These results are consistent with clinical findings of the importance of severe acid exposure[22,23] and reflux of duodenal contents[24–26] in the pathogenesis of Barrett's oesophagus.

Columnar epithelium has been reported to be inherently more resistant to acid than squamous epithelium[27,28]. Herbst *et al.* demonstrated that cell turnover is accelerated in Barrett's epithelium compared with squamous epithelium in the same patient[29]. These authors speculated that regeneration of columnar epithelium occurs more easily than that of squamous epithelium when both squamous and columnar cells are faced with erosion or ulceration, especially under conditions of high acidity.

Other studies, both clinical and experimental, have drawn attention to the origin of acquired oesophageal columnar epithelialization. The theory of upward extension of gastric mucosa replacing squamous epithelium was suggested by Endo *et al.*[30] and Hamilton and Yardley[8]. Berenson *et al.*[31] and Naef and colleagues[6] proposed metaplasia of squamous epithelium. Bremner *et al.*[13] and Wong and Finckh[32] supported the upward replacement theory, but Gillen *et al.*[14] pointed out that this mechanism could not explain the well known variety of epithelial patterns seen in Barrett's oesophagus[33]. By using squamous barriers to proximal migration of columnar epithelium in the stomach, they found that the cell of origin of the epithelium was located in oesophageal glands[14]. No evidence of metaplasia of squamous epithelium has, however, been demonstrated experimentally.

In the present study, columnar epithelium intermingled with squamous epithelium contained abundant goblet cells stained positively by alcian blue–PAS, and closely resembled intestinal epithelium. It appeared that the columnar epithelium had arisen from intestinal epithelium that infiltrated upwards to the distal oesophagus across the anastomosis. This finding supports the theory of upward extension. The islands of columnar epithelium surrounded by squamous epithelium were found distant from the site of anastomosis. What appeared to be glandular tissues were observed in the oesophageal epithelium. Rats, however, have no oesophageal glands[34,35]. Thus, it is possible that metaplastic change occurred in squamous epithelium during the course of regeneration in the animal model used.

Acknowledgements

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References

1. Barrett NR. Chronic peptic ulcer of the oesophagus and 'oesophagitis'. *Br J Surg* 1950; **38**: 175–82.
2. Allison PR, Johnstone AS. The oesophagus lined with gastric mucous membrane. *Thorax* 1953; **8**: 87–101.
3. Barrett NR. The lower oesophagus lined by columnar epithelium. *Surgery* 1977; **41**: 881–94.
4. Mossberg SM. The columnar-lined oesophagus (Barrett syndrome) – acquired condition? *Gastroenterology* 1966; **50**: 671–6.
5. Naef AP, Savary M. Conservative operations for peptic oesophagitis with stenosis in columnar-lined lower oesophagus. *Ann Thorac Surg* 1972; **13**: 543–51.
6. Naef AP, Savary M, Ozzello L. Columnar-lined lower oesophagus: an acquired lesion with malignant preposition. *J Thorac Cardiovasc Surg* 1975; **70**: 826–35.
7. Halvorsen JF, Semb BKH. The 'Barrett syndrome' (the columnar-lined lower oesophagus): an acquired condition secondary to reflux oesophagitis. *Acta Chirurgica Scandinavica* 1975; **141**: 683–7.
8. Hamilton SR, Yardley JH. Regeneration of cardiac type mucosa and acquisition of Barrett mucosa after esophagogastrostomy. *Gastroenterology* 1977; **72**: 669–75.
9. Messian RA, Hermos JA, Robbins AH, Fridlander DM, Schimmel EM. Barrett's oesophagus. *Am J Gastroenterol* 1978; **69**: 458–66.
10. Spechler SJ, Sperber H, Doos WG, Schimmel EM. The prevalence of Barrett's oesophagus in patients with chronic peptic oesophageal strictures. *Dig Dis Sci* 1983; **28**: 769–74.
11. Borrie J, Goldwater L. Columnar cell-lined oesophagus: assessment of aetiology and treatment. *J Thorac Cardiovasc Surg* 1976; **71**: 825–34.
12. Hennessy TPJ, Edlich RF, Buchin RJ, Tsung MS, Prevost M, Wangensteen OH. Influence of gastroesophageal incompetence. *Arch Surg* 1968; **97**: 105–7.
13. Bremner CG, Lynch VP, Ellis FH. Barrett's oesophagus: congenital or acquired? An experimental study of oesophageal mucosal regeneration in the dog. *Surgery* 1970; **68**: 209–16.
14. Gillen P, Keeling P, Byrne PJ, West AB, Hennessy TPJ. Experimental columnar metaplasia in the canine oesophagus. *Br J Surg* 1988; **75**: 113–15.
15. Ferguson DJ, Sanchez-Palomela E, Sako Y, Clatworthy HW, Toon RW, Wangensteen OH. Studies on experimental oesophagitis. *Surgery* 1950; **28**: 1022–39.
16. Cross FS, Wangensteen OH. Role of bile and pancreatic juice in production of oesophageal erosions and anaemia. *Proc Soc Exp Biol Med* 1951; **77**: 862–6.
17. Levrat M, Lambert R, Kirshbaum G. Esophagitis produced by reflux of duodenal contents in rats. *Am J Dig Dis* 1962; **7**: 564–73.
18. Kivilaakso E, Fromm D, Silen W. Effect of bile salts and related compounds on isolated oesophageal mucosa. *Surgery* 1980; **87**: 280–5.
19. Mud HJ, Kranendonk SE, Westbroek DL. Active trypsin and reflux oesophagitis: an experimental study in rats. *Br J Surg* 1982; **69**: 269–72.
20. Lillemoe KD, Johnson LF, Harmon JW. Alkaline oesophagitis: a comparison of the ability of components of gastroduodenal contents to injure the rabbit oesophagus. *Gastroenterology* 1983; **85**: 621–8.
21. Seto Y, Kobori O, Shimizu T, Morioka Y. The role of alkaline reflux in oesophageal carcinogenesis induced by *N*-amyl-*N*-methylnitrosamine in rats. *Int J Cancer* 1991; **49**: 758–63.
22. Iascone C, DeMeester TR, Little AG, Skinner DB. Barrett's oesophagus. *Arch Surg* 1983; **118**: 543–9.
23. Gillen P, Keeling P, Byrne PJ, Hennessy TPJ. Barrett's oesophagus: pH profile. *Br J Surg* 1987; **74**: 774–6.
24. Gillen P, Keeling P, Byrne PJ, Healy M, O'Moore RR, Hennessy TPJ. Implication of duodenogastric reflux in the pathogenesis of Barrett's oesophagus. *Br J Surg* 1988; **75**: 540–3.
25. Attwood SEA, DeMeester TR, Bremner CG, Barlow AP, Hinder RA. Alkaline gastroesophageal reflux: implications in the development of complications in Barrett's columnar-lined lower esophagus. *Surgery* 1989; **106**: 764–70.
26. Waring JP, Legrand J, Chinichian A, Sanowski RA. Duodenogastric reflux in patients with Barrett's oesophagus. *Dig Dis Sci* 1990; **35**: 759–62.
27. Kiriluk LB, Merendino KA. The comparative sensitivity of the mucosa of the various segments of the alimentary tract in the dog to acid–peptic action. *Surgery* 1954; **35**: 547–56.

28. Bremner CG. The columnar-lined (Barrett's) oesophagus. *Surg Annu* 1977; **9**: 103–23.
29. Herbst JJ, Berenson MM, McCloskey DW, Wiser WC. Cell proliferation in oesophageal columnar epithelium (Barrett's oesophagus). *Gastroenterology* 1978; **75**: 683–7.
30. Endo M, Kobayashi S, Kozu T, Takemoto T, Nakayama K. A case of Barrett epithelialization followed up for five years. *Endoscopy* 1974; **6**: 48–51.
31. Berenson MM, Herbst JJ, Freston JW. Enzyme and ultrastructural characteristics of oesophageal columnar epithelium. *Am J Dig Dis* 1974; **19**: 895–907.
32. Wong J, Finckh ES. Heterotopia and ectopia of gastric epithelium produced by mucosal wounding in the rat. *Gastroenterology* 1971; **60**: 279–87.
33. Paull A, Trier JS, Dalton MD, Camp RC, Loeb P, Goyal RK. The histologic spectrum of Barrett's oesophagus. *N Engl J Med* 1976; **295**: 476–80.
34. Goetsch E. The structure of the mammalian oesophagus. *Am J Anat* 1910; **10**: 1–40.
35. Trskova-Boselova L, Meitner ER. Komparative Mikromorphologie der Speiserohre einiger Wirbeltiere. *Anat Anz* 1974; **135**: 357–72.

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Announcement

The British Journal of Surgery Society SRS Prize

The British Journal of Surgery Society is to make a generous annual donation of £400 to the Surgical Research Society to be used as a prize. The Committee of the SRS, on behalf of its membership, is pleased to acknowledge the gift with gratitude.

The SRS Committee has decided that the prize will be awarded for the best paper published in the *BJS* that originates from an SRS presentation in the preceding year. The Committee of the SRS will judge these papers at its January meeting and the prize will be announced and presented at the dinner of the SRS.

The SRS is pleased to maintain close ties with the Journal. Two months each year are special SRS issues and contain most of the papers from presentations made to the SRS. It is hoped that this prize will encourage more presenters of SRS papers to prepare manuscripts without detracting from the principle of the SRS to enjoy receiving reports of work in progress. Papers not making publication in the SRS issues *will not be ineligible* and the winner of the Patey Prize *may* submit a paper and be equally eligible. It should be noted that any paper submitted as a result of presentation to the SRS passes through the same rigorous process of referee analysis and editorial criticism by the Journal; publication is not guaranteed.

SRS authors should identify the January or July meeting of the presentation on the submitted manuscript. Papers will automatically be collected and reviewed for the prize. Those already published in 1993 issues will automatically be included for consideration of the prize to be awarded for the first time in January 1994.

'Thank you' to The British Journal of Surgery Society for fostering and encouraging surgical research.

J. R. Farndon
Honorary Secretary
Surgical Research Society

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Incidence and management of benign anastomotic stricture after cervical oesophagogastrostomy

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Benign anastomotic stricture after transhiatal oesophagectomy and gastric tube reconstruction constitutes a major problem. From August 1988 to April 1991, 81 patients were followed after cervical oesophagogastrostomy. Twenty-four patients (30 per cent) developed a benign anastomotic stricture 3–23 (median 8) weeks after operation. Poor vascularization of the gastric tube, determined during operation, and postoperative anastomotic leakage were statistically significant risk factors for stricture formation. Symptoms related to stricture were often typical and were confirmed by endoscopy and/or radiography. Radiography did not yield information additional to that obtained from endoscopy. Strictures were treated in the outpatient clinic by dilatation with Savary dilators. Repeated dilatation completely alleviated dysphagia in 20 of the 24 patients (83 per cent). In ten patients dilatations could be discontinued after a median of 8 (range 1–17) sessions. Dilatation was continued until the end of follow-up in nine patients or until death from recurrent disease in five. No complications of dilatation were seen.

The development of benign anastomotic stricture after oesophageal and partial gastric resection constitutes a major problem. This complication has been reported to occur in 12–40 per cent of cases after cervical oesophagogastrostomy when using gastric pull-up or a gastric tube for reconstruction of the oesophagus[1–6]. Despite the occurrence of this complication, cervical anastomosis is favoured by many surgeons over intrathoracic anastomosis because of its low mortality rate following leakage[7,8].

When stricture is diagnosed, non-surgical treatment by endoscopic dilatation is thought to be the therapy of choice[9,10], even though data supporting dilatation of cervical anastomotic stricture are scarce. In most cases, dilatation is repeated frequently to relieve dysphagia.

This report describes benign anastomotic stricture in a series of patients who underwent total oesophagectomy and gastric tube reconstruction for cancer of the oesophagus and/or gastric cardia with regard to incidence, possible risk factors, diagnostic procedures and management.

Patients and methods

From August 1988 to April 1991, 85 patients underwent transhiatal oesophagectomy and partial gastrectomy for cancer of the oesophagus or oesophagocardiac region.

In all patients reconstruction was carried out using a 3-cm wide gastric tube fashioned along the greater curvature. The gastric tube was pulled gently through the thorax to the neck. Cervical anastomosis of the proximal oesophagus to the tube was performed manually, end to side, with a one-layer running suture of 3/0 Polydioxanone (Ethicon, Norderstedt, Germany). The gastric tube was of sufficient length in all patients to permit anastomosis without tension. In most patients the redundant length of gastric tube was resected.

All patients underwent radiographic examination (barium swallow) of the anastomosis between the seventh and tenth day after operation to establish patency and detect anastomotic leakage.

Patients were routinely seen in the outpatient clinic at 6 weeks and 3 months, at 3-month intervals for 1 year and at 6-month intervals thereafter. Follow-up was at least 26 weeks.

Patients were specifically questioned for problems related to swallowing. Severe dysphagia was defined as the inability to swallow solids and semisolids, and moderate dysphagia as the inability to take solids only.

The following were considered to be possible risk factors for anastomotic stricture and were analysed statistically: sex, age, length of operation, location of tumour (upper or middle *versus* distal third or cardia), histological type (adenocarcinoma *versus* squamous cell carcinoma), tumour node metastasis (TNM) stage (0–II *versus* III and IV)[11], postoperative gastric reflux (determined by the presence of typical symptoms and/or need for medical therapy), peroperative judgement by the surgeon of gastric tube vascularization (good *versus* poor), resection of redundant gastric tube after anastomosis, and postoperative anastomotic leakage. Anastomotic leakage was defined as that seen on radiography, or as a salivary fistula.

Three of the 85 patients suffered major dehiscence of the oesophagogastric anastomosis necessitating takedown of the anastomosis. The conduit was reconstructed by colonic interposition; these three patients were excluded from analysis. One patient died in the postoperative period, leaving 81 patients, 57 men and 24 women, of median age 65 (range 33–81) years at risk for benign cervical anastomotic stricture.

Patients with problems swallowing solids were evaluated endoscopically and radiographically in the outpatient clinic. If indicated, anastomotic strictures were biopsied to rule out tumour recurrence.

Strictures were treated conservatively with dilatation as described by Savary *et al.*[9]. Mild sedation with midazolam was used in some cases. Dilatation was repeated as indicated or until death from recurrent malignancy.

Cumulative freedom from anastomotic stricture was estimated on a Kaplan–Meier[12] plot. Different levels of possible risk factors were compared for the occurrence of anastomotic stricture using the univariate log rank test. Cox[13] multivariate proportional hazards regression analysis was then used to determine independent risk factors for the presence or absence of stricture.

Results

The characteristics of the 81 patients are shown in *Table 1*. Anastomotic stricture developed in 24 (30 per cent) between weeks 3 and 23 (median 8) after operation. The estimated cumulative stricture-free rate(s.e.) was 69(5·2) per cent after a follow-up of 26 weeks (*Figure 1*).

Table 1 also shows the relationship between possible risk factors and the development of a clinically apparent stricture.

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Table 1 *Univariate analysis for 81 patients at risk for anastomotic stricture*

	Stricture		
Risk factor	Yes ($n = 24$)	No ($n = 57$)	P*
Sex			
M	14 (25)	43 (75)	n.s.
F	10 (42)	14 (58)	
Mean age (years)			
<63	10 (29)	25 (71)	n.s.
≥63	14 (30)	32 (70)	
Length of operation (h)			
<4	19 (37)	33 (63)	n.s.
≥4	5 (17)	24 (83)	
Location of tumour			
Upper or middle	5 (22)	18 (78)	n.s.
Distal or cardia	19 (33)	39 (67)	
Histology			
Squamous cell carcinoma	12 (34)	23 (66)	n.s.
Adenocarcinoma	12 (26)	34 (74)	
TNM classification			
0–II	8 (35)	15 (65)	n.s.
III or IV	16 (28)	42 (72)	
Gastric reflux			
Yes	1 (14)	6 (86)	n.s.
No	23 (31)	51 (69)	
Vascularization of gastric tube			
Good	15 (22)	52 (78)	0·002
Poor	9 (64)	5 (36)	
Resection of redundant gastric tube			
Yes	18 (29)	45 (71)	n.s.
No	6 (33)	12 (67)	
Postoperative leakage			
Yes	8 (67)	4 (33)	0·004
No	16 (23)	53 (77)	

Values in parentheses are percentages. TNM, tumour node metastasis; n.s., not significant. *Log rank test

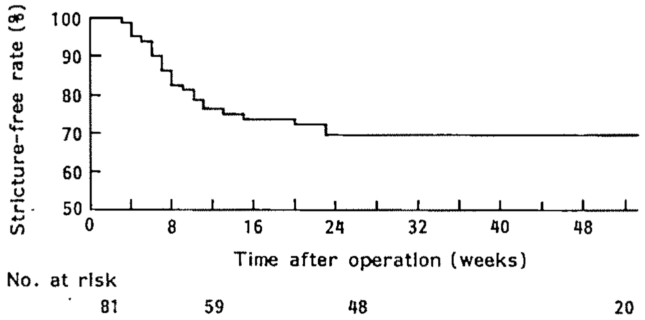

Figure 1 *Estimated cumulative percentage of patients free from stricture*

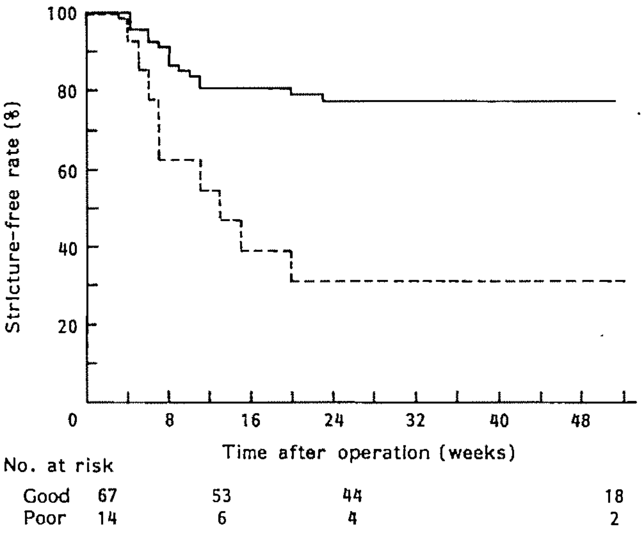

Figure 2 *Estimated cumulative percentage of patients free from stricture according to peroperative judgement of vascularization of the gastric tube.* ——, *Good vascularization* (n = *67*); - - -, *poor vascularization* (n = *14*)

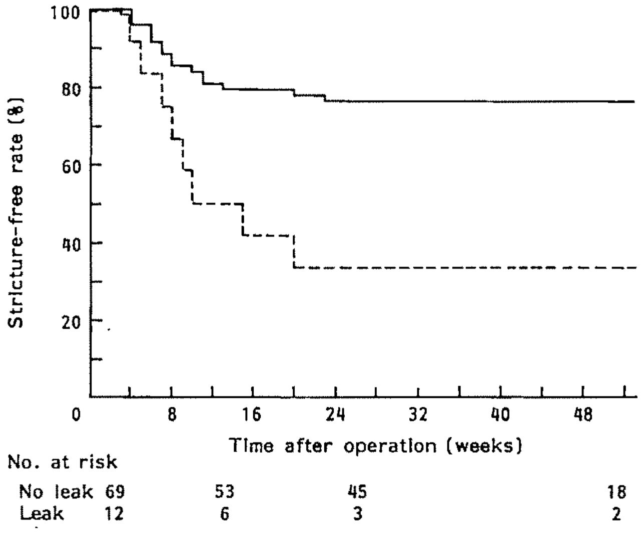

Figure 3 *Estimated cumulative percentage of patients free from stricture according to the presence of anastomotic leakage.* ——, *No leakage* (n = *69*); - - -, *leakage* (n = *12*)

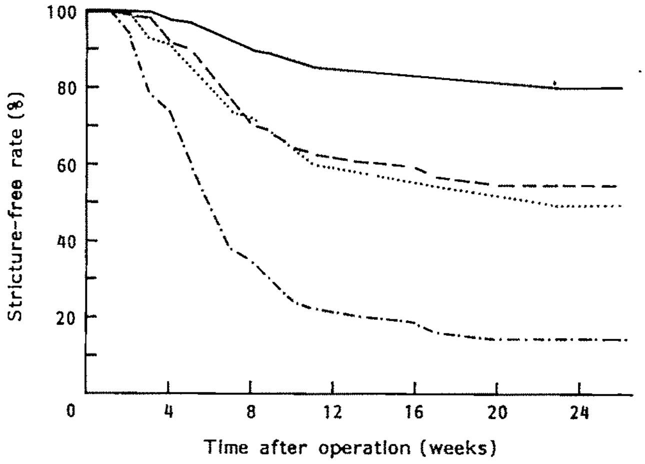

Figure 4 *Predicted cumulative percentage of patients free from stricture according to peroperative judgement of vascularization of the gastric tube and the presence of anastomotic leakage.* ——, *No leakage and good vascularization;* - - -, *leakage and good vascularization;* ....., *no leakage and poor vascularization;* — · —, *leakage and poor vascularization*

Only poor vascularization of the gastric tube and anastomotic leakage were associated with an increased risk for the development of stricture. The rate of anastomotic stricture in the presence of poor or good vascularization of the gastric tube is shown in *Figure 2*. *Figure 3* shows the estimated stricture rate in the presence or absence of anastomotic leakage. Cox proportional hazards analysis confirmed the significance of these risk factors (vascularization, $P = 0{\cdot}008$; anastomotic leakage, $P = 0{\cdot}025$).

The predicted anastomotic stricture rate in four different subgroups with regard to the significant risk factors from 1 to 26 weeks after operation is shown in *Figure 4*.

The diagnosis of anastomotic stricture was based on symptoms, endoscopy and radiography. Results of the diagnostic procedures are shown in *Table 2*. All patients with severe dysphagia developed anastomotic stricture confirmed on endoscopy or radiography. Only five of the 23 patients complaining of moderate dysphagia appeared to have stricture

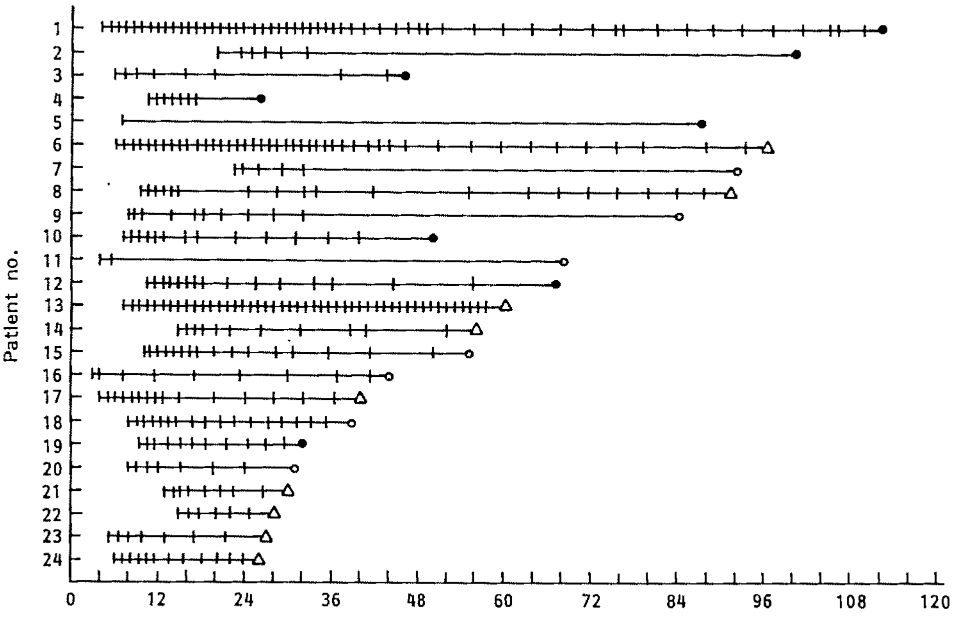

Figure 5 *Dilatation of benign anastomotic stricture showing period and frequency of treatment. State at end of study:* ●, *died;* ○, *alive;* △, *under treatment. Each vertical bar represents one session of dilatation*

Table 2 *Diagnostic procedures in patients with dysphagia after cervical oesophagogastrostomy*

Dysphagia	Stricture on radiography	Stricture on endoscopy
Moderate ($n = 23$)	3 of 23 (13)	5 of 23 (22)
Severe ($n = 19$)	17 of 17 (100)	19 of 19 (100)

Values in parentheses are percentages

on endoscopy; three of these strictures were also seen on radiography. Symptoms were not progressive in 18 patients with moderate dysphagia and could be managed by chewing solids thoroughly.

Endoscopic dilatation was performed in the 24 patients and was successful after a median of 9·5 (range 1–55) sessions in 20. Four patients continued to have moderate dysphagia after a median of 12 (range 2–47) sessions. Dilatation could be discontinued in ten patients after a median of 8 (range 1–17) sessions over a period of 1–45 weeks. In 14 patients, dilatation of the stricture with a frequency of one to four times per month was continued until death from recurrent disease (five patients) or until the end of the study period (nine) (*Figure 5*). No complications of dilatation were seen.

Discussion

The primary symptom in patients with an oesophageal tumour is dysphagia. If dysphagia returns after a major reconstructive procedure, a purely physical complication can turn into a psychological problem as well.

In this series the incidence of benign anastomotic stricture after cervical oesophagogastrostomy was 30 per cent. Others have reported an incidence of 12–40 per cent for a similar procedure[1–6]. Anastomotic stricture occurred 3–23 (median 8) weeks after operation. Sex, age, length of operation, location of tumour, histological type, tumour stage, gastric reflux and resection of the redundant proximal end of the gastric tube did not predict the development of stricture, but poor vascularization of the gastric tube and anastomotic leakage did.

Poor vascularization of the upper part of the gastric tube was noted by the surgeon in 14 patients, nine of whom developed stricture after operation. Four of these 14 patients had anastomotic leakage. In constructing the gastric tube from the greater curvature, three of the four major gastric arteries are sacrificed to obtain sufficient length to reach the neck and only the right gastroepiploic artery remains intact. However, at the proximal part of the gastric tube the gastroepiploic arcade is absent and vascularization depends solely on intramural blood vessels[14–16].

An advantage of the small diameter of the tube in comparison with total gastric pull-up, in which the right gastric artery may be preserved, is the low frequency of reflux[17].

Oesophageal vascularization has not been evaluated in this series and could be a risk factor for impaired anastomotic healing. This is not very likely, however, since intramural oesophageal vascularization is generally good[18].

Anastomotic leakage, occurring in 12 of the 81 patients (15 per cent), is another risk factor for the development of stricture. Leakage was clinically evident in ten patients. Eight of the 12 patients with leakage developed anastomotic stricture. The predicted cumulative rate of freedom from anastomotic stricture in patients with poor vascularization and anastomotic leakage was 14 per cent after 26 weeks (*Figure 4*). If both risk factors were absent, 80 per cent of the patients were predicted to be free from stricture after 26 weeks. This suggests additional factors that might explain the development of cervical anastomotic stricture.

The influence of the anastomotic technique (manual or stapled) on stricture formation and leakage is unclear[19–21]. A manual one-layer anastomosis with continuous 3/0 Polydioxanone has been used in different kinds of intestinal anastomosis and has proven reliable.

None of the five patients with an intrathoracic oesophagogastrostomy operated on in the same period as the present patients developed anastomotic stricture. The low incidence of stricture in intrathoracic anastomosis is confirmed by the experience of one of the present authors (H.O.) in another series of patients with oesophageal cancer; stricture did not occur after intrathoracic anastomosis using similar surgical techniques[22]. Other authors have reported similar results[8,23] and it is possible that the pleural mesothelium may improve healing of the anastomosis. The oesophagus is not covered by a serosal layer and the cervical anastomosis is not surrounded by mesothelial cells. Despite a higher incidence of impaired anastomotic healing, cervical oesophagogastrostomy is favoured by most surgeons because of the low mortality rate accompanying anastomotic leakage[8,9]. Cervical leakage usually leads to a temporary salivary fistula that heals without invasive therapy, whereas mediastinal leakage has more serious consequences[2,4,5].

Barium swallow and endoscopy were performed in patients with symptoms of dysphagia (*Table 2*). If a patient complained of severe dysphagia and could swallow only fluids, an anastomotic stricture was always detected by endoscopy and radiography. In 23 patients with moderate dysphagia able to pass semisolids and fluids, a stricture was present (and dilatation necessary) in five. Radiography did not yield information additional to that from endoscopy in patients with problems swallowing and, in all cases where the patient has to undergo endoscopy for dilatation, radiography is superfluous.

Once a stricture has been diagnosed as non-malignant several treatment options are available[24–30]. Because of its simplicity and safety, endoscopic dilatation as described by Savary *et al.*[9,24] was chosen for the present series. The procedure was performed on an outpatient basis and lasted approximately 15 min. Dilatation was generally well tolerated and mild sedation necessary only occasionally. In most patients the procedure had to be repeated frequently (*Figure 5*), but complete relief of dysphagia was obtained in 20 of the 24 patients and in ten treatment could be permanently discontinued after a median of 8 (range 1–17) sessions. Success rates varying from 61 to 88 per cent have been reported using different techniques of dilatation, although none of these reports addressed cervical anastomotic stricture specifically[10,25–27]. No complications occurred in a total of 351 sessions of Savary dilatation. Even though dilatation could not be discontinued in 14 of the 24 patients, it appears to be an effective alternative to surgical intervention because of the small amount of time involved, and its safety and ease of application.

References

1. Orringer MB. Transhiatal esophagectomy without thoracotomy for carcinoma of the thoracic esophagus. *Ann Surg* 1984; **200**: 282–8.
2. Tilanus HW, Langenhorst BLAM. Morbidity and mortality after oesophageal resection without thoracotomy. *Gullet* 1991; **1**: 122–5.
3. Mahoney JL, Condon RE. Adenocarcinoma of the oesophagus. *Ann Surg* 1987; **205**: 557–62.
4. Collard J, Otte JB, Reynaert M, Michel L, Carlier MA, Kestens PJ. Esophageal resection and bypass: a 6 year experience with low postoperative mortality. *World J Surg* 1991; **15**: 635–41.
5. von Christ F, Janson R, Kunath U, Engel C. Der intrathorakal-extrapleurale Ösophagusersatz durch Magenplastik. *Fortschr Geb Rontgenstr Nuklearmed Ergamzungsbd* 1984; **141**: 666–73.
6. Wang L-S, Huang M-H, Huang B-S, Chien K-Y. Gastric substitution for resectable carcinoma of the oesophagus: an analysis of 368 cases. *Ann Thorac Surg* 1992; **53**: 289–94.
7. Lorentz T, Manson FRCS, Fok M, Wong J. Anastomotic leakage after resection and bypass for esophageal cancer: lessons learned from the past. *World J Surg* 1989; **13**: 472–7.
8. Chasseray VM, Kiroff GK, Buard JL, Launois B. Cervical or thoracic anastomosis for esophagectomy for carcinoma. *Surg Gynecol Obstet* 1989; **169**: 55–62.
9. Savary M, Haury JA, Monnier Ph. Les troubles de la déglutition: diagnostic et traitement. *Rev Med Suisse Romande* 1986; **106**: 313–41.
10. Wesdorp ICE, Bartelsman JFWM, den Hartog Jager FCA, Huibregtse K, Tytgat GN. Results of conservative treatment of benign esophageal strictures: a follow-up study in 100 patients. *Gastroenterology* 1982; **82**: 487–93.
11. Union Internacional Contra la Cancrum. *TNM Classification of Malignant Tumours*. Geneva: UICC, 1968.
12. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–81.
13. Cox DR. Regression models and life-tables. *J R Stat Soc (B)* 1972; **34**: 187–220.
14. Agossou-Voyème AK, Hureau J, Germain M. Arterial vascularization of the operated stomach: highly selective vagotomy, anterior lesser curve seromyotomy, esophageal replacement by transposed stomach after esophagectomy or circular pharyngolaryngectomy. *Surg Radiol Anat* 1990; **12**: 247–57.
15. Akiyama H. *Surgery for Cancer of the Esophagus*. Baltimore, Maryland: Williams and Wilkins, 1990: 54–9.
16. Dei Poli M, Albertino B, Spalluto F *et al.* Gastric angiography: data for oesophagogastroplasty. *Panminerva Medica* 1990; **32**: 61–4.
17. Obertop H. Problems after esophageal surgery for cancer. In: Tytgat GNJ, van Blankenstein M, eds. *Current Topics in Gastroenterology and Hepatology*. Stuttgart: Georg Thieme Medical, 1990: 160–3.
18. Liebermann-Meffert DMI, Luescher U, Neff U, Rüedi TP, Allgöwer M. Esophagectomy without thoracotomy: is there a risk of intramediastinal bleeding? *Ann Surg* 1987; **206**: 184–92.
19. Hopkins RA, Alexander JC, Postlethwait RW. Stapled esophagogastric anastomosis. *Am J Surg* 1984; **147**: 283–7.
20. Wong J. Stapled esophagogastric anastomosis in the apex of the right chest after subtotal esophagectomy for carcinoma. *Surg Gynecol Obstet* 1987; **164**: 568–72.
21. Lam TCF, Fok M, Cheng SWK, Wong J. Anastomotic leakage following oesophageal reconstruction using whole stomach or distal stomach. *Gullet* 1991; **1**: 114–18.
22. Eeftinck Schattenkerk M, Obertop H, Mud HJ, Eijkenboom WMH, van Andel JG, van Houten H. Survival after resection for carcinoma of the oesophagus. *Br J Surg* 1987; **74**: 165–8.
23. Moorehead RJ, Wong J. Gangrene in esophageal substitutes after resection and bypass procedures for carcinoma of the esophagus. *Hepatogastroenterology* 1990; **37**: 364–7.
24. Shemesh E, Czerniak A. Comparison between Savary and balloon dilatation of benign esophageal strictures. *World J Surg* 1990; **14**: 518–21.
25. Benedict EB. Peptic stenosis of the esophagus – a study of 233 patients treated with bougienage, surgery or both. *Am J Dig Dis* 1966; **11**: 761–70.
26. Lanza FL, Graham DY. Bougienage is an effective therapy for most benign esophageal strictures. *JAMA* 1978; **240**: 844–7.
27. Aste H, Munizzi F, Saccomanno S, Pugliese V. 'Splitting' and stretching dilatation of esophageal strictures. *Endoscopy* 1983; **15**: 41–3.
28. Lilly JO, McCaffrey TD Jr. Esophageal stricture dilation: a new method adapted to the fibreoptic esophagoscope. *Am J Dig Dis* 1971; **16**: 1137–40.
29. Sali A. Dilations of oesophageal strictures. In: Jamieson GG, ed. *Surgery of the Oesophagus*. London: Churchill Livingstone, 1988: 831–43.
30. Celestin LR, Campbell WB. A new and safe system for oesophageal dilatation. *Lancet* 1981; **i**: 74–5.

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Norwegian multicentre study of survival and prognostic factors in patients undergoing curative resection for gastric carcinoma

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The influence of clinical and tumour-related variables on long-term survival in patients with gastric carcinoma was studied in a national prospective multicentre study. A total of 532 patients underwent curative surgery with a 5-year survival rate of 40 per cent. In a Cox multivariate analysis, age, stage of disease and macroscopic appearance of tumour were the only factors that independently affected survival. The estimated probability of survival to 5 years for a 50-year-old patient with a flattened tumour type and stage I disease was 71 per cent, but 50 per cent for an 80-year-old with the same tumour type and stage. For stage II disease the rates were 56 and 32 per cent, for stage III 39 and 13 per cent and for stage IV 19 and 3 per cent, respectively. A 70-year-old patient with stage II linitis plastica tumour type had an estimated probability of 5-year survival of 20 per cent. Stage of disease was the single most important factor in determining survival. Laurén histopathological type and location of tumour, Karnofsky performance index, weight loss and type of resection had no significant effect on long-term survival.

The prognosis for patients with gastric cancer in the western world remains dismal. This contrasts with results from Japan, where a steady overall improvement and increased 5-year survival rate for all stages of the disease has occurred[1–4]. Some authors have tried to identify subgroups of patients with survival characteristics similar to those in Japan[5–8]. Others question whether gastric cancer in Japan and the western world represent different biological forms.

Most authors agree that stage of disease is the critical factor in predicting survival. Japanese surgeons have standardized and implemented meticulous and extensive operative procedures; the benefit in terms of better long-term survival remains unproven[9]. Direct comparison of results is difficult for several reasons: lack of a uniform definition of curative surgery; differences in staging systems; selection bias caused by the nature of studies (retrospective *versus* prospective); and inappropriate application of analytical methods[8,9].

The present study was performed to evaluate the influence of factors related to the patient, tumour and operative procedure on the prognosis of patients with gastric cancer entered into a large prospective national multicentre study. The follow-up was at least 5 years.

Patients and methods

The Norwegian Stomach Cancer Trial is a prospective multicentre study with 51 surgical units participating. The design of the study was observational, each hospital recording clinical and histopathological data that were submitted for central computation and analysis. Patients were recruited from September 1982 to December 1984. In that period 1165 patients had been included, representing 54 per cent of all those with gastric cancer registered by the cancer registry of Norway. Detailed short-term results have been reported previously[10–13].

Resection was classified by the attending surgeon as: (1) potentially curative, i.e. no macroscopic residual lesion, and tumour-free resection margins; (2) palliative, i.e. residual tumour or distant metastases; or (3) technically impossible, or patient inoperable for other reasons. Of the 1165 patients entered into the trial, 532 with adenocarcinoma underwent potentially curative resection and form the basis of the present study.

Disease was staged according to the tumour node metastasis (TNM) system[14] and histological subtyping was as described by Laurén[15]. Lymph node involvement was categorized as n1 (perigastric nodes along the lesser and greater curvature) or n2 (paragastric nodes along the coeliac axis and its trifurcation). Involvement of other intra-abdominal lymph nodes (n3) is now regarded as distant metastasis[16].

Survival data for all patients were obtained from the cancer registry of Norway. Follow-up was ended in December 1989 after at least 5 years. Univariate survival analyses were performed by the Kaplan–Meier method[17]. The log rank (Mantel–Cox) test was used for statistical comparison of survival probabilities. Univariate analyses were performed for age, sex, hospital level (university, county or local), weight loss, Karnofsky index, delays in treatment caused by patient or doctor, gastric remnant cancer, type of resection, splenectomy, tumour site, TNM classification, Laurén histological type, gross macroscopic tumour appearance (polypoid, flattened, linitis plastica) and size, and ABO and rhesus blood groups. All factors were included in a Cox proportional hazards model[18]. To check the proportionality assumption and best fit, a log-minus-log survival function was requested for each stratum (variable). By a backwards stepping procedure, the least significant variable or first-order interaction was eliminated at each step. The variables remaining in the final model were included in a forward stepping procedure. Both approaches gave identical results and the final Cox model was based on 513 evaluable patients. The regression coefficients were assessed for significance using the likelihood ratio test. Computations were performed using the Bio Medical Data Program (BMDP Statistical Software, Los Angeles, California, USA) package[19].

Results

Patients undergoing curative resection

The median age of the patients, comprising 319 men and 213 women, was 70 years; 40 per cent survived for 5 years (*Figure 1*). The survival rates for subgroups of patients and for all those included in the trial are given for comparison. The 5-year survival rate for all patients with adenocarcinoma ($n = 1104$) was 19 per cent. Of those undergoing palliative resection, 6 per cent survived for 5 years. No patient with irresectable disease survived >20 months.

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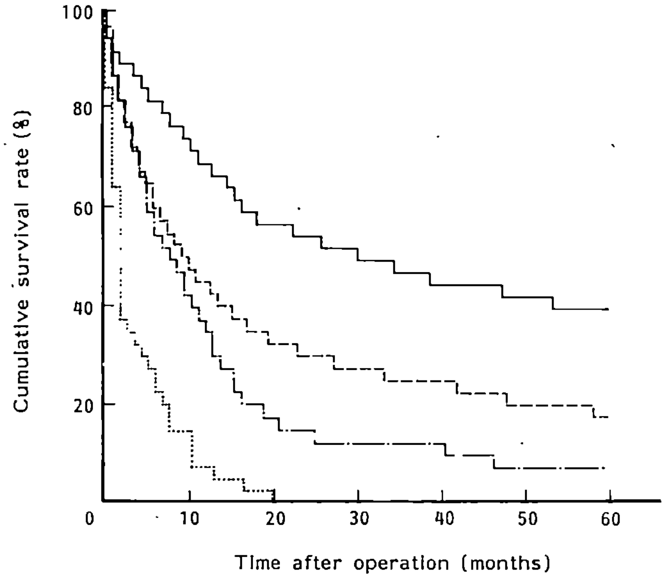

Figure 1 *Univariate analysis of survival related to extent of operation for gastric carcinoma.* ——, *All patients;* ——, *curative resection;* — · —, *palliative resection;* ·····, *no operation or palliative procedure*

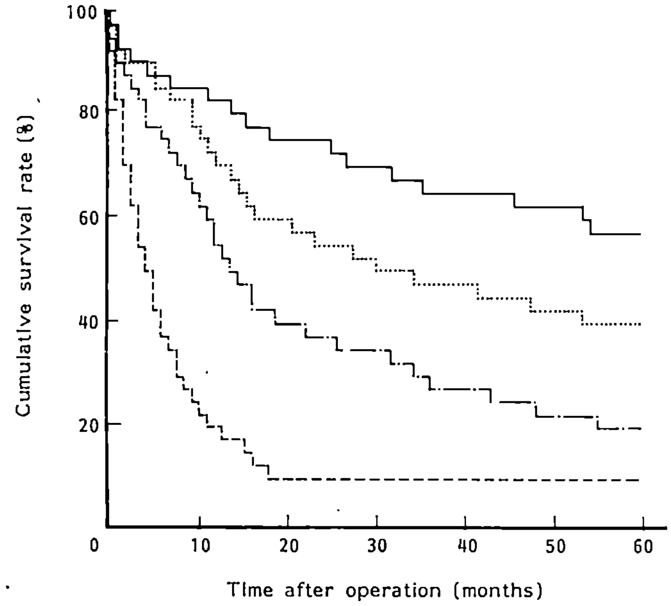

Figure 2 *Univariate analysis of survival related to stage of gastric carcinoma.* ——, *Stage I;* ·····, *stage II;* — · —, *stage III;* ——, *stage IV*

Univariate analysis

A total of 61 per cent of patients with stage I cancer ($n = 201$) survived 5 years (*Figure 2*). This was reduced to 40 per cent for stage II disease ($n = 130$), 20 per cent for stage III ($n = 179$) and 9 per cent for stage IV ($n = 22$).

The 5-year survival rate according to clinicopathological variables is shown in *Table 1*. No significant differences in 5-year survival rates were found with regard to delay in treatment introduced by patient or doctor, Laurén histological type, ABO or rhesus blood groups, gastric remnant cancer or whether or not splenectomy was performed (data not given).

Multivariate analysis

Of ten clinicopathological variables that influenced survival on univariate analysis (*Table 1*), only age, stage of disease and macroscopic appearance of tumour independently affected survival (*Table 2*). The most important variable was stage of disease; survival declined for every stage increment ($P < 0{\cdot}0001$). To illustrate the independent effect of age and stage of disease, a probability of 5-year survival for every tumour stage given a flattened tumour type and for different age categories was estimated. A 50-year-old patient with a flattened tumour type had an estimated probability of 5-year survival of 71 per cent with stage I disease (*Figure 3*), 56 per cent with stage II, 39 per cent with stage III and 19 per cent with stage IV (*Figure 4*).

Patients with the flattened type tumour had better survival than those with the polypoid and linitis plastica types ($P = 0{\cdot}002$, *Figure 5*).

Increasing age led to poorer 5-year survival rates ($P = 0{\cdot}0005$). An 80-year-old patient with stage I disease and a flattened tumour type had a probability of 5-year survival of 50 per cent, compared with 71 per cent at age 50 years. The difference in 5-year survival probability between these two age groups was 24 per cent for stage II tumours (56 *versus*

Table 1 *Univariate analysis of 5-year survival according to clinical and pathological variables*

	No. of patients	Survival rate (%)	P*
Sex			
M	319	38	0·03
F	213	43	
Age (years)			
≤49	30	53	0·0005
50–59	76	51	
60–69	153	46	
70–79	195	34	
≥80	78	28	
Stage of disease†			
I	201	61	<0·0001
II	130	40	
III	179	20	
IV	22	9	
Weight loss (kg)			
0	220	45	0·006
1–5	102	44	
6–10	99	27	
>10	35	23	
Karnofsky index			
≤70	64	23	<0·0001
71–80	94	24	
81–90	180	47	
91–100	139	49	
Operative procedure			
Proximal resection	14	21	0·04
Distal resection	155	45	
Subtotal gastrectomy	108	43	
Total gastrectomy	255	37	
Hospital level			
County	116	46	0·007
University	233	42	
Local	183	34	
Tumour location			
Fundus	88	36	<0·0001
Fundus and corpus	39	23	
Corpus	68	54	
Corpus and antrum	57	40	
Antrum	238	45	
All regions	33	15	
Macroscopic type			
Flattened	356	45	0·0005
Polypoid	93	30	
Linitis plastica	17	0	
Length of tumour (mm)			
≤20	100	53	0·006
21–40	144	42	
41–60	132	35	
61–80	66	30	
81–100	25	44	
>100	19	21	

*Log rank test. †Tumour node metastasis classification

Table 2 *Cox proportional hazards model of factors affecting survival*

	Coefficient(s.e.)	P*	Coefficient/ s.e.	Hazard ratio
Age (years)				
x (any age)				
$x+10$	0·203(0·058)	0·0005	3·502	1·271
Stage of disease†				
x (any stage)				
$x+\mathrm{I}$	0·598(0·065)	<0·0001	9·260	1·818
Macroscopic type				
Flattened				
Polypoid	0·437(0·142)	0·002	3·074	1·548
Linitis plastica	0·515(0·219)		2·348	1·676
Hospital level‡				
County				
University	0·246(0·151)	0·05	1·627	1·279
Local	0·368(0·153)		2·397	1·444

*Likelihood ratio test. †Tumour node metastasis classification. ‡Hospital level was not included in the final model

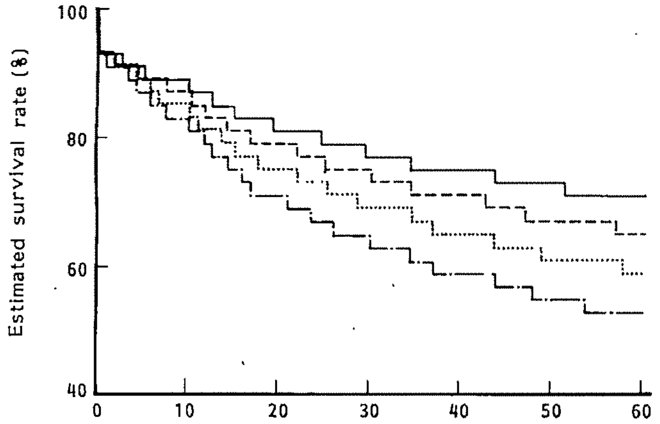

Figure 3 *Survival rate estimated for patients of different age groups with stage I gastric carcinoma and tumour of flattened macroscopic type.* ——, *50 years;* ——, *60 years;* ·····, *70 years;* —·—, *80 years*

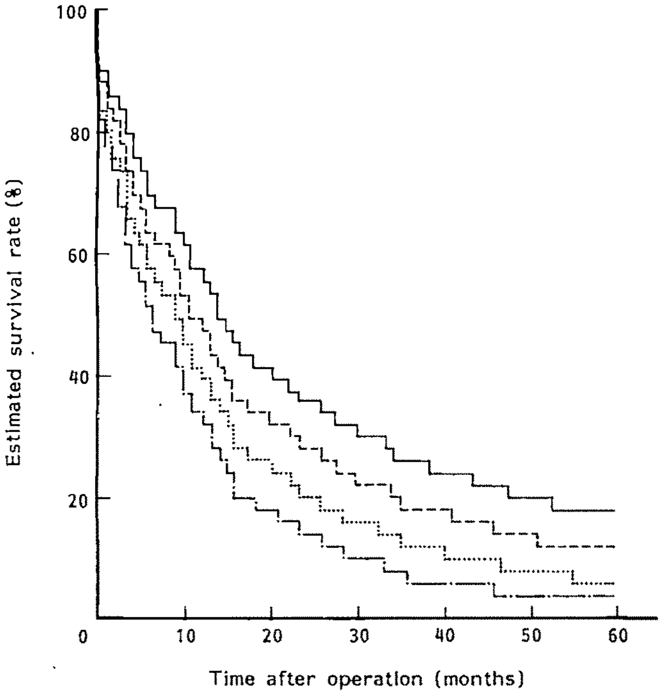

Figure 4 *Survival rate estimated for patients of different age groups with stage IV gastric carcinoma and tumour of flattened macroscopic type.* ——, *50 years;* ——, *60 years;* ·····, *70 years;* —·—, *80 years*

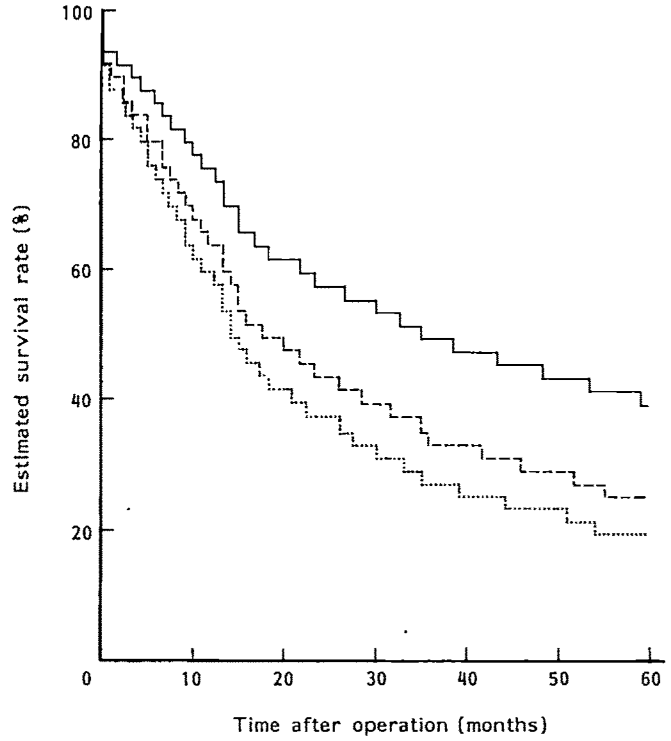

Figure 5 *Survival rate estimated for patients with different macroscopic tumour types aged 70 years and with stage II gastric carcinoma.* ——, *Flattened;* ——, *polypoid;* ·····, *linitis plastica*

32 per cent), 26 per cent for stage III (39 *versus* 13 per cent) and 16 per cent for stage IV (19 *versus* 3 per cent).

Hospital level was found to be of borderline significance as an independent prognostic factor ($P = 0·05$). Patients operated on in county hospitals had a better 5-year survival rate than those undergoing surgery in local or university hospitals. A patient aged 65 years with stage III disease and a flattened macroscopic tumour type had a 30 per cent probability of survival to 5 years if treated in a county hospital, 26 per cent if treated in a university hospital and 20 per cent if treated in a local hospital.

Discussion

The problem of postoperative complication and death has been discussed previously[8]. The present analysis failed to demonstrate that the extent of gastric resection was a significant predictor of long-term survival. These results corroborate findings by Msika and co-workers[5]. Shiu *et al.*[20], however, pointed to a survival advantage for less extensive operations. They studied 246 patients retrospectively in whom lesions of the cardia and gastro-oesophageal junction were excluded. Even if the present analysis was restricted to patients with tumours of the antrum, there was still no statistically significant difference in 5-year survival rate between distal resection and total gastrectomy (data not shown).

In the present univariate analyses distal resection was associated with the best 5-year survival rate (*Table 1*); this does not take into account differences in patient and tumour characteristics between the various treatment groups. It is felt, with others[3,5,8], that multivariate studies using the Cox model should be the standard for survival analysis. According to this approach there was no statistically significant difference in survival between the various gastric resections.

An important consideration during surgery for gastric carcinoma is whether splenectomy is necessary to ensure a curative operation. The incidence of metastases to splenic hilar nodes correlates with tumour site[20] and splenectomy has been advocated on a routine basis except for antral tumours. The present study revealed that removal of the spleen carried no survival advantage. This is in accordance with results from others[20,21]. Contradictory data have, however, been published[22].

The essence of the present study is that stage of disease is the most important factor predicting survival, as shown by others[1,3,5,8]. The 5-year survival figures are comparable to those in recent western reports[5,20]; 61 per cent of patients with stage I disease survived 5 years. This is still below that found in Japanese series[23,24] and may result from the meticulous lymph node dissection carried out by Japanese surgeons, which secures a more accurate staging[25]. Since the 5-year survival rates for stage III and IV disease are comparable to Japanese results the main effect of radical lymphadenectomy is a more accurate staging. The effect of the extended operation itself may be of limited importance for long-term survival, but may reduce the number of patients developing local recurrence[26,27]. Two ongoing randomized clinical trials (the Medical Research Council Surgical Gastric Cancer Trial in the UK and a Dutch trial) that address the problem of regional lymphadenectomy (R_2 resection) may provide definite answers.

Okada *et al.*[1] and Maruyama[3] have shown in two retrospective series that the macroscopic tumour appearance was an independent prognostic factor. This is confirmed in the present study and indicates a need for a supplement to the TNM classification system.

Laurén histopathological type[15] was not an independent prognostic factor for survival. This is in accordance with results from Rohde *et al.*[28] in a prospective multicentre study from Germany.

The present study did not reveal any difference in 5-year survival rates between proximally or distally located tumours. A retrospective report from Maruyama[3] contradicts this, while others[1,5] agree.

This study has shown that surgery-related variables did not affect long-term survival in patients with gastric carcinoma. The survival data raise the question of whether there is any long-term survival advantage from extended surgery, as claimed by Japanese surgeons. The poor prognosis of patients with gastric carcinoma in Norway is related to advanced stages of disease, high age and unfavourable macroscopic type.

Acknowledgements

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References

1. Okada M, Kojima S, Murikami M *et al.* Human gastric carcinoma: prognosis in relation to macroscopic and microscopic features of the primary tumor. *J Natl Cancer Inst* 1983; **75**: 275–8.
2. Baba H, Korenaga D, Okamura T, Saito A, Sugimachi K. Prognostic factors in gastric cancer with serosal invasion. *Arch Surg* 1989; **124**: 1061–4.
3. Maruyama K. The most important prognostic factors for gastric cancer patients. A study using univariate and multivariate analyses. *Scand J Gastroenterol* 1987; **22**: 63–8.
4. Boku T, Nakane Y, Okusa T *et al.* Strategy for lymphadenectomy of gastric cancer. *Surgery* 1989; **105**: 585–92.
5. Msika S, Chastang C, Houry S, Lacaine F, Huguier M. Lymph node involvement as the only prognostic factor in curative resected gastric carcinoma: a multivariate analysis. *World J Surg* 1989; **13**: 118–23.
6. Higgins GA, Serlin O, Amadeo JH, McElhinney J, Keehn J. Gastric cancer: factors in survival. *Surgical Gastroenterology* 1976; **10**: 393–8.
7. Bozzetti F, Bonfanti G, Morabito A *et al.* A multifactorial approach for the prognosis of patients with carcinoma of the stomach after curative resection. *Surg Gynecol Obstet* 1986; **162**: 229–34.
8. Søreide O, Lillestøl J, Viste A, Bjerkeset T. Factors influencing survival in patients with cancer of the stomach: a multivariate analysis. *Acta Chirurgica Scandinavica* 1982; **148**: 367–72.
9. Cuschieri A. Gastrectomy for gastric cancer: definitions and objectives. *Br J Surg* 1986; **73**: 513–14.
10. Valen B, Viste A, Haugstvedt TK, Eide GE, Søreide O. Treatment of stomach cancer. A national experience. *Br J Surg* 1988; **75**: 708–12.
11. Viste A, Haugstvedt TK, Eide GE, Søreide O. Postoperative complications and mortality after surgery for gastric cancer. *Ann Surg* 1988; **207**: 7–13.
12. Haugstvedt T, Viste A, Eide GE, Søreide O. Survival benefit of resection in patients with advanced stomach cancer: the Norwegian multicentre experience. *World J Surg* 1989; **13**: 617–22.
13. Haugstvedt TK, Viste A, Eide GE, Søreide O. Factors related to and consequences of weight loss in patients with stomach cancer: the Norwegian multicentre experience. *Cancer* 1991; **67**: 722–9.
14. Hermanek P, Sobin LH. *TNM Classification of Malignant Tumors.* Berlin: Springer-Verlag, 1987.
15. Laurén P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. *Acta Pathol Microbiol Scand* 1965; **64**: 31–49.
16. Japanese Research Society for Gastric Cancer. The general rules for the gastric cancer study in surgery and pathology. *Jpn J Surg* 1981; **11**: 127–45.
17. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457.
18. Cox DR, Oakes D. *Analysis of Survival Data.* London: Chapman and Hall, 1984.
19. Dixon WJ, Brown MB, Engelman L *et al. BMDP Statistical Software.* Berkeley, California: University of California Press, 1985: 557–94.
20. Shiu MH, Moore E, Sanders M *et al.* Influence of the extent of resection on survival after curative treatment of gastric carcinoma. *Arch Surg* 1987; **122**: 1347–51.
21. Noguchi Y, Imada T, Matsumoto A, Coit D, Brennan MF. Radical surgery for gastric cancer. A review of the Japanese experience. *Cancer* 1989; **64**: 2053–62.
22. Toge T, Hamamoto S, Itaga E, Nakane H, Yajima K, Hattori T. Analysis of suppressor cell activity in spleen cells from gastric cancer patients and the effect of splenectomy on prognosis of gastric cancer. *Nippon Geka Gakkai Zasshi* 1983; **84**: 961–4.
23. Maruyama K. *Survival Treatment and End Results of Gastric Cancer.* Tokyo: National Cancer Center, 1985.
24. Koga S, Kishimoto H, Tanaka K *et al.* Results of total gastrectomy for gastric cancer. *Am J Surg* 1980; **140**: 636–8.
25. Kodama Y, Sugimachi K, Soejima K, Matsusaka T, Inokuchi K. Evaluation of extensive node dissection for carcinoma of the stomach. *World J Surg* 1981; **5**: 241–8.
26. Phillips RKS. Staging systems and data analysis. *Scand J Gastroenterol* 1987; **22**: 14–16.
27. Meyer HJ, Pichlmayr R. Patterns of recurrence in relation to therapeutic strategy in gastric cancer. *Scand J Gastroenterol* 1987; **22**: 45–8.
28. Rohde H, Gebbensleben B, Bauer P, Stützer H, Zieschang J. Has there been any improvement in the staging of gastric cancer? Findings from the German Gastric Cancer TNM Study Group. *Cancer* 1989; **64**: 2465–81.

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Vagal system involvement in changes in small bowel motility during restraint stress: an experimental study in the dog

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Changes in small intestinal motility were studied during restraint stress in fasting animals and after food; the involvement of the vagal system in the pathophysiology of these changes was assessed. Small intestinal motility was recorded in 40 dogs using electromyography with monopolar electrodes and manometry with submucosal microballoons. Twenty animals underwent bilateral truncal vagotomy. Stress increased intestinal motility (percentage of slow waves followed by action potentials in 1 min), both in fasting conditions ($P < 0{\cdot}001$) and postprandially ($P < 0{\cdot}001$). It also completely abolished the migrating motor complex–interdigestive myoelectric complex periodicity characteristic of the normal fasting pattern. In dogs subjected to vagotomy, restraint stress increased motility during fasting ($P < 0{\cdot}001$) but decreased it after feeding ($P < 0{\cdot}01$). Restraint stress thus increases small intestinal motility, both during fasting and after food. The vagal system is partially involved in this hypermotility response.

A problem encountered frequently in general medicine and gastroenterology is the patient with functional digestive disease[1–3]. Many patients report emotional conflicts that coincide with the onset of symptoms, or their domestic, social or working life is characterized by constant stress[4–10]. On the other hand, various clinical and experimental studies have related stress to functional digestive syndromes and alterations in gastrointestinal motility[11–14]. Involvement of the colon is now well established in irritable bowel syndrome[5,15–21], and the stomach appears to play an important role in the high functional dyspepsia syndrome[22]. However, involvement of the small intestine in the pathophysiology of these syndromes has been studied to a lesser extent, possibly owing to the limitations of exploring the motility of this segment of bowel[23].

The aims of the present study were: (1) to describe alterations in small intestinal motility in response to restraint stress during fasting and after feeding; and (2) to analyse the involvement of the vagal nervous system in these alterations. To record intestinal motility, electromyography with monopolar electrodes and manometry with submucosal microballoons were used[24,25].

Materials and methods

Materials

Animals. Forty adult mongrel dogs weighing between 5 and 12 kg were divided into groups to study: (1) the effect of restraint stress on intestinal motility, during fasting (group 1; $n = 10$) and after food (group 2; $n = 10$); and (2) the effect of restraint stress on intestinal motility in dogs that had undergone vagotomy, during fasting (group 3; $n = 10$) and after food (group 4; $n = 10$).

To eliminate the possibility of the dogs becoming accustomed to stress, 40 animals were used for 40 experiments, so that each dog was exposed to stress only once.

Intestinal electromyography and manometry. The recording apparatus consisted of monopolar electrodes with a silver chloride needle for recording electrical activity and latex microballoons for recording pressure activity. An eight-channel polygraph (model 7758 D System; Hewlett–Packard, Madrid, Spain) equipped with three bioelectrical amplifiers and three pressure amplifiers was used.

Surgery and anaesthesia. The necessary surgical equipment for performing a small laparotomy was used. Anaesthesia was achieved with sodium pentobarbitone, 75 mg per kg body-weight. Respiratory function was maintained during anaesthesia with a Manley-type paediatric ventilator.

Methods

Surgical technique. Under strict asepsis a small midline laparotomy was performed. The recording apparatus was placed at three sites in the small intestine: the second part of duodenum, ligament of Treitz and proximal jejunum, spaced 30 cm apart. The electrodes were sutured to the intestinal serosa with 4/0 silk. At the same sites microballoons were placed in a submucosal tunnel[26] (*Figure 1*). During the same laparotomy, bilateral truncal vagotomy was carried out on the 20

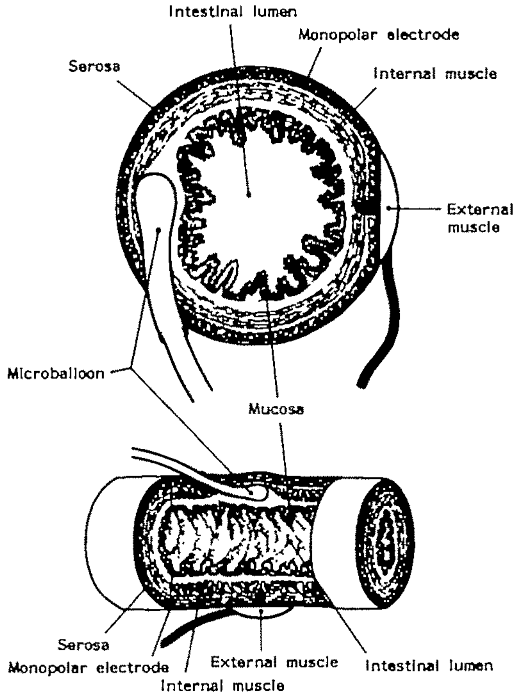

Figure 1 *Position of the electrode and microballoon in the intestinal wall*

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animals in groups 3 and 4. Vagotomy was confirmed in all cases by histological examination.

Experimental design. At 10 days after operation and after fasting for 24 h, the animal was connected to the polygraph and two control interdigestive myoelectric complexes (IMCs) were recorded. A standardized stress stimulus was applied at the selected time for a period that depended on the experimental group. In groups 1 and 3, the stimulus was applied during phase I of the IMC and 10 min after recording the end of phase III respectively. It was maintained for 4 h in group 1 and for 2 h in group 3. In groups 2 and 4, the stimulus was applied after feeding, for 2 h.

The standardized restraint stress stimulus consisted of complete immobilization of the neck, body and legs of the dog in plaster. Once the animal had been disconnected from the polygraph, it was held steady and wrapped with cotton bandages and strips of fresh plaster. No precast plastic shells were used to maximize immobilization, nor was any sedative or anaesthesia acting on the central nervous system administered, so as not to interfere with any possible stress action.

The protocol was approved by the animal research committee in accordance with current legislation governing the use of animals in experiments.

Intestinal motility recordings. The recordings were studied in two ways: (1) by observing changes caused by restraint stress on fasting and postprandial patterns. In fasting animals, persistence of the characteristic phase III of the IMC[25] was noted; (2) by quantifying intestinal motility as the percentage of slow waves followed by action

Table 1 *Effect of restraint stress on intestinal motility under basal conditions (control group) and in dogs undergoing vagotomy, both fasting and after food*

	Action potential: slow wave ratio (%)	
	Before stress	During stress
Fasting		
Control (group 1; $n = 10$)		
Duodenum	3·10(1·95)	84·43(11·00)*
Ligament of Treitz	3·06(1·36)	86·20(11·67)*
Jejunum	3·00(1·18)	84·44(12·89)*
Vagotomy (group 3; $n = 10$)		
Duodenum	3·20(0·67)	13·52(8·46)*
Ligament of Treitz	3·29(0·90)	21·77(9·26)*
Jejunum	3·32(0·80)	24·67(7·10)*
After food		
Control (group 2; $n = 10$)		
Duodenum	47·56(9·34)	83·86(8·27)*
Ligament of Treitz	46·72(9·13)	81·26(10·34)*
Jejunum	51·62(15·10)	81·18(7·83)*
Vagotomy (group 4; $n = 10$)		
Duodenum	45·18(10·95)	36·05(7·13)†
Ligament of Treitz	47·96(7·72)	36·36(6·28)†
Jejunum	49·26(3·76)	34·25(8·40)†

Values are mean(s.d.). *$P < 0·001$; †$P < 0·01$ (before stress *versus* during stress, analysis of variance)

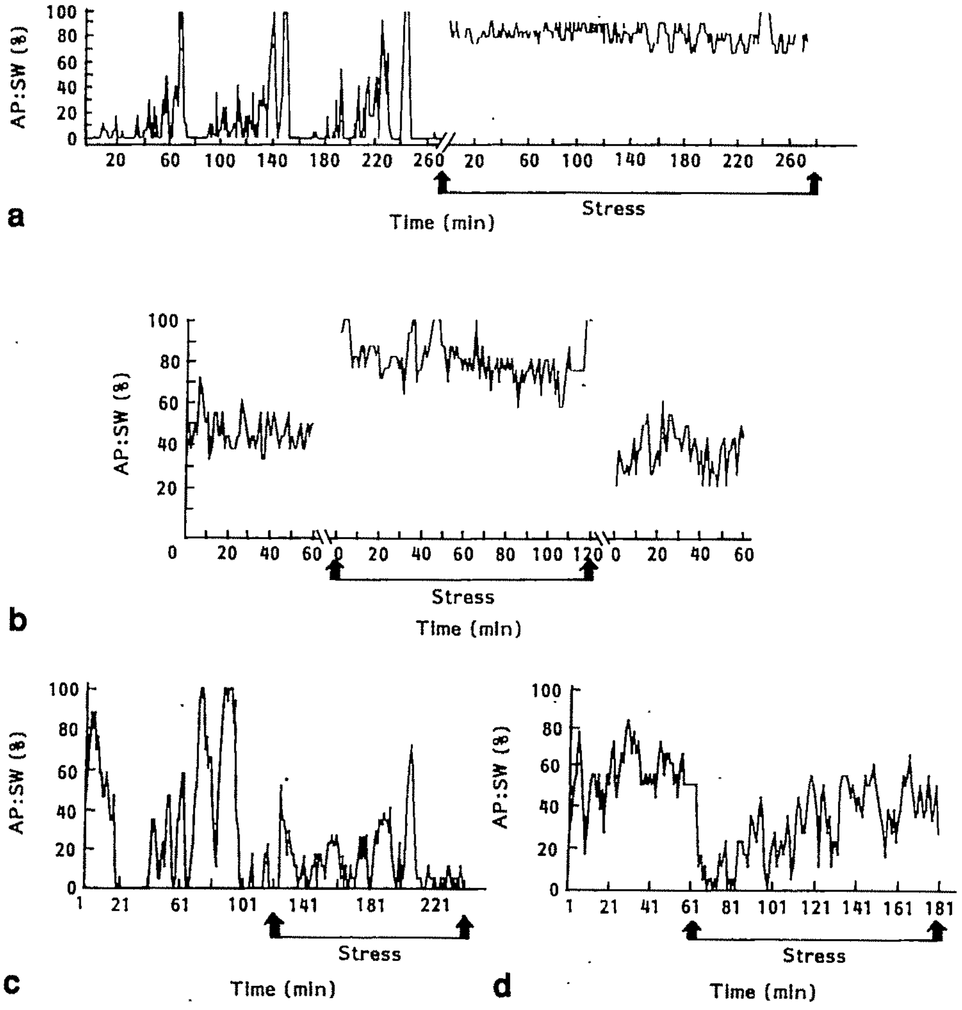

Figure 2 *Effect of restraint stress on intestinal motility expressed as the action potential:slow wave ratio (AP:SW).* **a** *Under basal conditions during fasting there is a significant increase in motility and complete abolition of the fasting motor pattern.* **b** *Under basal conditions after food there is a significant increase in the motility rate during stress.* **c** *In dogs undergoing vagotomy, during fasting there is an increase in motility. This increase is significantly lower than that observed in control dogs during stress. In seven of the ten recordings complete abolition of the fasting motor pattern was observed.* **d** *In dogs undergoing vagotomy, after food hypomotility is produced during stress, i.e. an effect opposite to that observed in control dogs*

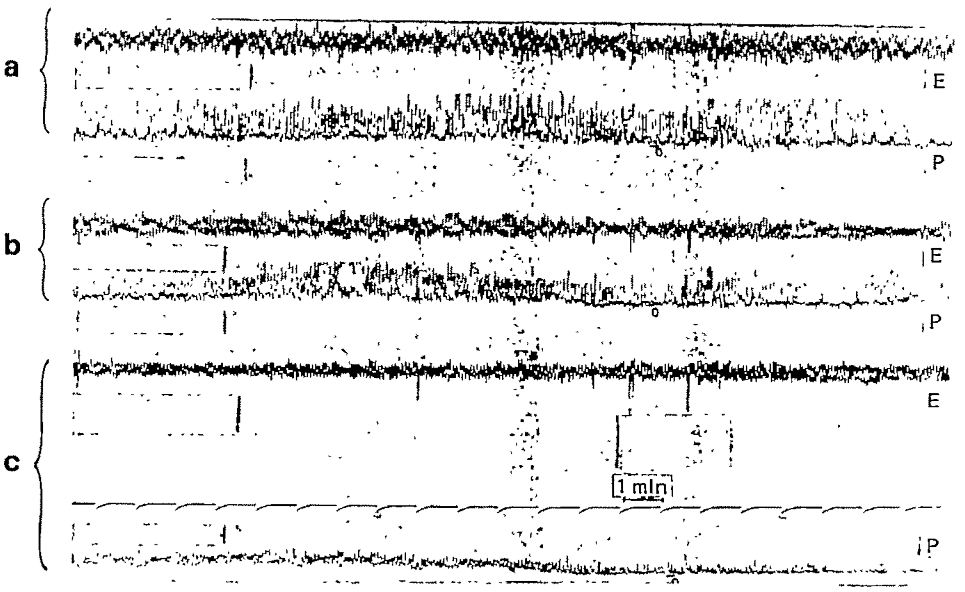

Figure 3 *Electromyographic and manometric recordings during fasting in stressed animals. Electrical (E) and pressure (P) activity are recorded simultaneously at the three different small intestinal sites:* **a** *duodenum;* **b** *ligament of Treitz;* **c** *jejunum. Stress-induced hypermotility is shown; the stress stimulus was applied 10 min before the recording*

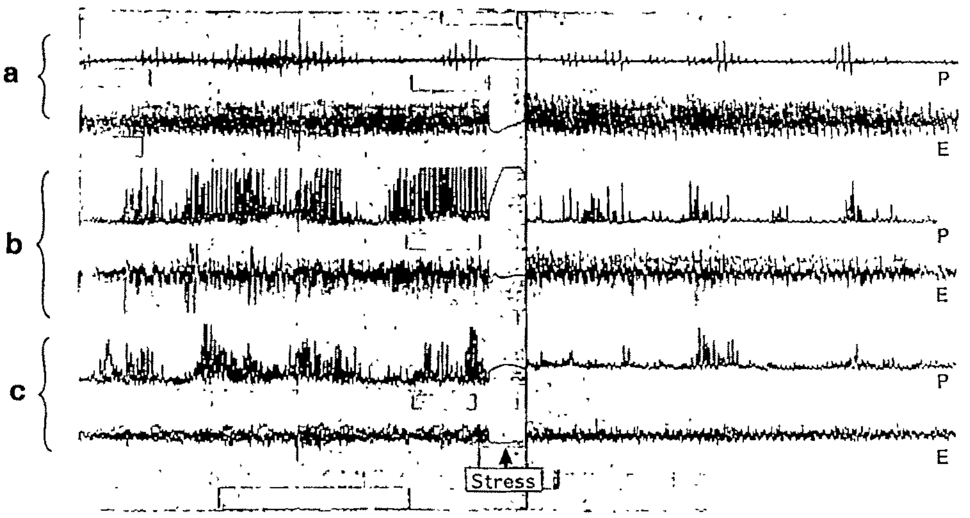

Figure 4 *Postprandial electromyographic and manometric recordings in dogs undergoing vagotomy before and during stress.* **a** *Duodenum;* **b** *ligament of Treitz;* **c** *jejunum. P, pressure activity; E, electrical activity. A hypomotility effect is shown*

potentials in 1 min, expressed according to the equation:

$$\text{AP:SW ratio} = \frac{\text{no. of action potentials in 1 min}}{\text{no. of slow waves in 1 min}} \times 100$$

The AP:SW ratio is a quantitative parameter of intestinal motility in a particular segment for this 1 min. The action potential, also known as a 'spike', consists of a single or multiple (but always rapid) variation in electrical activity; it does not always appear but, when it does, it is always related to the slow wave and located on the positive side[24].

Statistical analysis. Statistical treatment of data consisted of analysis of variance. Analyses used in all experimental groups corresponded to a factorial design, which considered the different factors that can influence variability in intestinal motility: animals, evolution with time and intestinal segment. Analyses of variance were carried out with significance tables using Tukey's partial comparison method[27].

Results

Effects of restraint stress on intestinal motility in dogs not undergoing vagotomy (control groups 1 and 2)

Restraint stress produced complete abolition of the characteristic migrating motor complex (MMC) of the normal fasting-pattern (*Figure 2a*) and an increase in the AP:SW ratio at the three levels studied. These differences were significant compared with phase I motility seen during fasting ($P < 0{\cdot}001$) (*Table 1; Figures 2a* and *3*) and postprandial motility ($P < 0{\cdot}001$) (*Table 1; Figure 2b*). The increased motility was maintained as long as the stress stimulus was applied (*Figures 2a* and *2b*).

Effects of restraint stress on intestinal motility in dogs undergoing vagotomy (groups 3 and 4)

During fasting (group 3), restraint stress produced a significant increase ($P < 0{\cdot}001$) in the AP:SW ratio compared with phase I motility at the three levels studied. This was maintained throughout application of the stress stimulus (*Table 1; Figure 2c*). The increase in motility was lower than the hypermotility of control group 1 ($P < 0{\cdot}001$). Furthermore, in three of the ten recordings propulsive motor fronts with similar characteristics to MMC phase III were recognized.

After food (group 4), restraint stress caused a significant decrease in the AP:SW ratio at the three levels studied ($P < 0{\cdot}01$) (*Table 1; Figures 2d* and *4*).

Discussion

It is currently accepted that different types of stress, both physical and mental, can alter gastrointestinal motor function in humans and animals[13,28,29]. Some frequently used models of mental stress are acoustic stress (deafening music, noises)[30,31], solving difficult anagrams[32], visual tests of driving in the city or with asteroids[11,33] and immobilization[34]. Among the existing models of physical stress are standardized pain stimuli[35], cold[1] and maze stimuli[13].

In the present paper the restraint stress model used caused a significant increase in intestinal motility both during fasting and after feeding. Various authors have described a hypermotility effect caused during fasting by different stress models, both mental[36] and physical[1,11,35,37,38]. Stress-induced changes in MMC–IMC periodicity have also been described[30–33,39–41]. McRae *et al.*[39] and Parnham and colleagues[40] observed a significant decrease in this periodicity in humans, whereas Kumar and Wingate[11] found complete abolition of MMCs in humans during the stress period, in line with the present results.

The present data support the studies of Gue *et al.*[42], who described a postprandial increase in motility during acoustic stress in the dog. By contrast, others[35] have described intestinal hypomotility, using a physical stress model. These differences may be the result of the use of different stress models. Physical stress could predominantly activate the adrenergic system and induce such a hypomotility effect[43]. Although the present, painless, stress model may activate the adrenergic system, it must have a more important influence on the vagal and β-endorphinergic systems, thus explaining the occurrence of the intestinal hypermotility effect.

On the other hand, the present experiments show that stress-induced intestinal hypermotility is partially inhibited by vagotomy, both during fasting and after feeding (*Figure 2*), indicating that the vagal system is directly involved in the motor response of the small intestine to restraint stress. There are known to be anatomical connections between the central nervous system and the intestine through the vagal system[44], such that the stress stimulus through the vagal fibres would induce the increase in intestinal motility and the disorganization of the fasting pattern[45–49]. As explained above, the painless stress model used in the present experiments could activate the vagal and β-endorphinergic systems and also the adrenergic system. Following vagotomy, restraint stress would activate only the adrenergic system, with appearance of the hypomotility effect.

In conclusion, these results show that restraint stress induces an increase in intestinal motility, both during fasting and after feeding, and that the vagal system is involved in this effect. The results cannot be extrapolated to humans because the stress applied to dogs may not be an effective model for stress in humans. However, clinical digestive syndromes may be triggered by aetiological mechanisms dependent on mental stress, and it is well known that intense emotion may be manifest as abdominal pain and diarrhoea. The physiological basis for such symptoms may be the hypermotility shown in these experiments.

References

1. Abbot FK, Mack M, Wolf S. The relation of sustained contraction of the duodenum to nausea and vomiting. *Gastroenterology* 1952; **20**: 238–48.
2. Mendelof AI. Epidemiology of functional gastrointestinal disorders. In: Chey WY, ed. *Functional Disorders of the Digestive Tract.* New York: Raven Press, 1983: 13–20.
3. Thompson WG, Heaton KW. Functional bowel disorders in apparently healthy people. *Gastroenterology* 1980; **79**: 283–8.
4. Abell TL, Kim CH, Malagelada JR. Idiopathic cyclic nausea and vomiting: a disorder of gastrointestinal motility. *Mayo Clin Proc* 1988; **63**: 1169–75.
5. Almy TP, Abbot FK, Hinkle JR. Alterations in colonic function in man under stress. Hypomotility of the sigmoid, and its relationship to the mechanism of functional diarrhea. *Gastroenterology* 1950; **15**: 84–94.
6. Almy TP. The gastrointestinal tract in man under stress. In: Sleisenger MH, ed. *Gastrointestinal Disease.* Philadelphia, Pennsylvania: WB Saunders, 1978: 3–19.
7. Almy TP. Therapeutic strategy in stress-related digestive disorders. *Clin Gastroenterol* 1977; **6**: 709–22.
8. Almy TP. Clinical features and diagnosis of functional gastrointestinal disorders. In: Chey WY, ed. *Functional Disorders of the Digestive Tract.* New York: Raven Press, 1983: 7–12.
9. Miller NE. Effect of learning on gastrointestinal function. *Clin Gastroenterol* 1977; **6**: 533–46.
10. Whitehead WE, Schuster MM. Behavioral approaches to the treatment of gastrointestinal motility disorders. *Med Clin North Am* 1981; **65**: 1397–411.
11. Kumar D, Wingate DL. The irritable bowel syndrome: a paroxysmal motor disorder. *Lancet* 1985; **ii**: 973–7.
12. McRae S, Thompson DG, Wingate DL, Younger K. Changes in the pattern of fasting jejunal motor activity during mental stress. *J Physiol (Lond)* 1980; **308**: 25.
13. Stanghellini V, Malagelada JR, Zinsmeister AR, Go VLW, Kao PC. Stress-induced gastroduodenal motor disturbance in humans: possible humoral mechanism. *Gastroenterology* 1983; **85**: 83–91.
14. Thompson DG, Richelson E, Malagelada JR. Perturbation of gastric emptying and duodenal motility throughout the central nervous system. *Gastroenterology* 1982; **83**: 1200–6.
15. Almy TP, Tulin M. Alterations in man under stress. Experimental production of changes simulating the 'irritable colon'. *Gastroenterology* 1947; **8**: 616–26.
16. Bassotti G, Pelli MA, Morelli A. Duodenojejunal motor activity in patients with chronic dyspeptic symptoms. *J Clin Gastroenterol* 1990; **12**: 17–21.
17. Drossman DA, Powell DW, Sessions JT. The irritable bowel syndrome. *Gastroenterology* 1977; **73**: 811–22.
18. Latimer PR. Irritable bowel syndrome: psychophysiological aspects. In: Chey WY, ed. *Functional Disorders of the Digestive Tract.* New York: Raven Press, 1983: 311–20.
19. Latimer P, Sarna S, Compbess D, Latimer M, Waterfall W, Daniel EE. Colonic motor and myoelectrical activity: a comparative study of normal subjects, psychoneurotic patients and patients with irritable bowel syndrome. *Gastroenterology* 1981; **80**: 893–901.
20. Murney RG, Winship PH. Sindrome de colon irritable. In: Conell QM, ed. *Clinica Gastroenterologica, Trastornos de la Motilidad.* Barcelona: Salvat, 1984: 124–55.
21. Sullivan MA, Cohen S, Snape WJ. Colonic myoelectrical activity in irritable bowel syndrome. *N Engl J Med* 1978; **298**: 878–83.
22. Malagelada JR, Stanghellini V. Manometric evaluation of functional upper gut symptoms. *Gastroenterology* 1985; **88**: 1223–31.
23. McCallum LW. Diagnosing motility disorders of the upper gastrointestinal tract. *South Med J* 1964; **77**: 947–55.
24. Bass P. Electric activity of smooth muscle of gastrointestinal tract. *Gastroenterology* 1965; **49**: 391–4.
25. Ponce JL. Motilidad del intestino delgado. Un metodo para el estudio dê la actividad electrica del intestino delgado (electroenterograma) y mecanica (manometrìa con sonda-microbalón submucoso) en el perro consciente. *PhD Thesis.* University of Murcia, 1980.
26. Code CF, Marlett JA. Modern medical physiology. Canine tachygastria. *Mayo Clin Proc* 1947; **49**: 325–32.
27. Domenech JM. *Bioestadistica. Metodos Estadisticos para Investigadores.* 2nd ed. Barcelona: Herder, 1977.
28. Stern RM. Responsiveness of the stomach to environmental stress. In: Hall R, Whitehead WE, eds. *Psychophysiology of the Gastrointestinal Tract: Experimental and Clinical Applications.* New York: Plenum, 1983: 181–207.
29. Wolf S, Wolf HG. *Human Gastric Function.* New York: Oxford University Press, 1947.
30. Gue M, Bueno L. Diazepam and muscimol blockade of the gastrointestinal motor disturbances induced by acoustic stress in dogs. *Eur J Pharmacol* 1986; **131**: 123–7.
31. Gue M, Pascaud X, Honde C, Junjen JL, Bueno L. Peripheral antagonist action of trimebutine and κ opioid substances on acoustic stress-induced gastric motor inhibition in dogs. *Eur J Pharmacol* 1988; **146**: 57–63.
32. Holtmann G, Singer MV, Kriebel R, Stacker KH, Goebell H. Differential effects of acute mental stress on interdigestive secretion of gastric acid, pancreatic enzymes and gastroduodenal motility. *Dig Dis Sci* 1989; **34**: 1701–7.
33. Valori RM, Kumar D, Wingate DL. Effects of different types of stress and of 'prokinetic' drugs on the control of fasting motor complex in humans. *Gastroenterology* 1986; **90**: 1890–900.
34. Lenz HJ, Burlage M, Raedler A, Greten H. Central nervous system effects of corticotropin-releasing factor on gastrointestinal

transit in the rat. *Gastroenterology* 1988; **94**: 598–602.
35. Parrilla P, Ramirez P, Muelas MS *et al.* Changes in small intestinal motility in acute physical stress. An experimental study. *Hepatogastroenterology* 1990; **37**: 140–6.
36. Roth HP, Ferreri RN, Petti MA, Evans MW. Motility of the small intestine during emotional reactions. *Ann Intern Med* 1953; **38**: 38–52.
37. Garcia D, Parrilla P, Ponce JL, Castellanos G, Martinez ML, Puig M. Dolor y alteración de la motilidad intestinal. Estudio experimental en perros. *Gastroenterologia y Hepatologia* 1983; **6**: 57–61.
38. Ramirez P. Alteraciones de la motilidad del intestino delgado en situaciones de stress fisciso agudo. Estudio experimental en perros. *PhD Thesis*. University of Murcia, 1986.
39. McRae S, Younger K, Thompson DG, Wingate DL. Sustained mental stress alters human jejunal motor activity. *Gut* 1982; **23**: 404–9.
40. Parnham AP, Patrick MP, Raiman A, Valori RL, Wingate DL. The inhibition of the human fasting motor complex by prolonged but intermittent mental stress. *J Physiol (Lond)* 1982; **332**: 100.
41. Wingate DL. Motility disorders of the small intestine in functional intestinal disorders. *Presse Med* 1989; **18**: 290–3.
42. Gue M, Peeters T, DePoortère I, VanTrappen G, Bueno L. Stress-induced changes in gastric emptying, postprandial motility and plasma gut hormone levels in dogs. *Gastroenterology* 1989; **97**: 1101–7.
43. Ramirez P, Muelas MS, Parrilla P *et al.* Papel de las catecolaminas en la hipomotilidad intestinal inducida por stress en situaciones de postingesta. Estudio experimental en perros. *Rev Esp Enferm Dig* 1987; **72**: 590–4.
44. Broks FP. Central nervous system and the digestive tract. In: Chey WY, ed. *Functional Disorders of the Digestive Tract.* New York: Raven Press, 1983: 21–8.
45. Daniel EE. Pharmacology of adrenergic, cholinergic, and drugs acting on other receptors in gastrointestinal muscle. In: Bertaccini G, ed. *Mediators and Drugs in Gastrointestinal Motility. II.* Heidelberg: Springer-Verlag, 1982: 249–322.
46. Daniel EE, Fox JET, Oki M *et al.* Study of peptides in control of motility. In: Chey WY, ed. *Functional Disorders of the Digestive Tract.* New York: Raven Press, 1983: 103–12.
47. Koo M, Ogle C, Cho C. The effect of cold-restraint stress on gastric emptying in rats. *Pharmacol Biochem Behav* 1985; **23**: 969–72.
48. Diamant NE, Hall K, Muy H, Elsharkawy TY. Vagal control of the feeding motor pattern in the lower esophageal sphincter, stomach and small intestine of dog. In: Christensen J, ed. *Gastrointestinal Motility.* New York: Raven Press, 1980: 365–70.
49. Weisbrodt NW. Effect of vagotomy on electrical activity of the small intestine of the dog. *Am J Physiol* 1975; **228**: 650–4.

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Announcement

Eurosurgery '93

The 3rd European Congress of Surgery under the auspices of Eurosurgery will take place in London from 14 to 17 September 1993. This international congress embraces all the specialties within surgery and sessions will be sponsored by all of the surgical specialist associations and societies of the participating nations, ensuring that there will be an international and multidisciplinary approach to many common surgical problems. Additionally, there will be European symposia of general interest to all surgeons on themes such as endoscopy, management of patients with trauma, daycase surgery, graduated patient care, surgical audit and surgery in the developing world. A major session on surgical training is also being organized by the surgical trainees' associations.

A large number of free papers will also be given and these communications will be published in a special supplement of *The British Journal of Surgery.*

On 14 September 1993 a number of satellite sessions sponsored by companies are being organized for delegates.

Further details and registration forms may be obtained from the Congress Secretariat, Eurosurgery 1993, Conference Associates and Services Ltd, Congress House, 55 New Cavendish Street, London W1M 8RE, UK. Telephone: 071 436 0531. Facsimile: 071 935 7559.

J. P. S. Lumley

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Obesity: an important prognostic factor in acute pancreatitis

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Ninety-nine patients with acute pancreatitis in whom body mass index ($BMI = weight\ (kg)/height^2\ (m^2)$) was measured were studied prospectively to determine the importance of obesity as a prognostic factor in this disease. Of 19 obese patients ($BMI \geqslant 30\ kg/m^2$), 12 developed severe pancreatitis; seven had abscesses, of whom five died, and two further patients died. In 80 non-obese patients, the incidence of severe pancreatitis (n = 5)*, abscess formation* (n = 4) *and death* (n = 4) *was significantly less* ($P = 0{\cdot}0007$)*. The mean(s.d.) BMI of 17 patients with severe acute pancreatitis was significantly higher than that in 82 patients with mild acute disease (31·2(5·6)* versus *23·3(5·6) kg/m²,* $P < 0{\cdot}001$)*. As a single prognostic factor, obesity had a sensitivity of 63 per cent and a specificity of 95 per cent for predicting disease severity. When five obese women with gallstone pancreatitis were excluded, the sensitivity of obesity increased to 86 per cent. Severe pancreatitis occurred in all eight obese patients with disease of an alcoholic aetiology. These data suggest that increased fat deposits in the peripancreatic and retroperitoneal spaces in obese patients may increase the risk of peripancreatic fat necrosis, abscess and death. Consideration should be given to including obesity as a prognostic factor in acute pancreatitis.*

Most patients who develop severe pancreatitis have evidence of pancreatic and peripancreatic necrosis. This would appear to be responsible for most of the local infective complications that culminate in multiple organ failure and death. The factors that promote this process are, however, obscure. A study of pancreatic resection in severe acute pancreatitis showed that most necrosis involved the peripancreatic tissue, with sparing of the pancreatic core[1]. It is conceivable that the extent of necrosis is increased by excessive peripancreatic fat deposits in the retroperitoneal space in obese patients, a view supported by the greater incidence of extensive peripancreatic necrosis[2] and systemic complications[3,4] in overweight individuals. This study was undertaken to investigate the link between obesity and necrosis, and to assess the value of body mass index (BMI) as an early prognostic indicator in acute pancreatitis.

Patients and methods

A study was made of 133 consecutive patients admitted with a first or second attack of acute pancreatitis to Groote Schuur Hospital during two periods: October 1988 to July 1989 and February to July 1990. These patients had a typical clinical presentation[5], supported by a serum amylase concentration >400 units/l (reference range <130 units/l), or evidence of acute pancreatitis at laparotomy or necropsy.

Clinical assessment of obesity was made where possible by the same observer and anthropometric measurements taken. Patients were weighed within 24 h of admission in hospital gowns on a seated scale; for those in intensive care a crane bedscale was used. Height was measured supine. BMI was calculated using the formula[6,7]:

$$BMI = weight\ (kg)/height^2\ (m^2)$$

Patients were classified[8] as underweight ($BMI < 19\ kg/m^2$), of normal weight (19–25 kg/m²), overweight (26–29 kg/m²) or obese ($\geqslant 30\ kg/m^2$). The outcome of each cohort was analysed separately.

Patients were assessed according to clinical and biochemical criteria, the modified Imrie scoring system[9] being used to assist in the assessment of disease severity. Measurement of blood lipid levels was employed only when the aetiological factors were not clearly identified. Severe pancreatitis was defined by the development of pancreatic necrosis, abscess, systemic organ failure requiring intensive care management, or death. Patients with suspected severe pancreatitis underwent standard computed tomography (CT) to assess the nature and extent of local pancreatic complications, but the diagnosis of infected pancreatic necrosis or pancreatic abscess was made at operation and supported by positive microbiological culture. Contrast-enhanced CT was not routinely used to assess pancreatic necrosis. The term pancreatic phlegmon was used when a large pancreatic mass was present on CT.

The clinical course, investigations, complications and interventions were documented in all patients until death or discharge from hospital. Data were entered into a database and analysed by Student's *t* test, Fisher's exact test and χ^2 analysis. The study was approved by the Ethics Research Committee of the University of Cape Town.

Results

Of the 133 patients admitted, 34 are not considered further because BMI measurements were not available, leaving 99 in the study group. Eighty-three patients were suffering their first attack of pancreatitis and the remaining 16 their second. There were 68 men and 31 women of mean(s.d.) age 41·2(12·7) years. The aetiology was alcoholic in 72 patients (61 men, 11 women), gallstone-induced in 14 (four men, ten women) and idiopathic in seven (two men, five women). Four attacks were associated with *Ascaris* infestation, one with hyperlipidaemia and one occurred after cholecystectomy.

Severe pancreatitis

Seventeen patients (17 per cent) developed severe pancreatitis, of whom 11 died. These 17 comprised 13 men of mean age 45 years and four women of mean age 40 years. The aetiology among the women was different from that among the men. One woman had pancreatitis associated with *Ascaris* infestation, one had hyperlipidaemia, disease in one followed cholecystectomy and in the fourth was idiopathic. None had alcoholic or gallstone pancreatitis. By contrast, only one of the men had idiopathic pancreatitis, disease in the rest being of alcoholic aetiology.

All 17 patients required intensive care for systemic complications. These included respiratory failure in all, renal failure in 12 and cardiac failure requiring inotropes in 14. Local complications included infected pancreatic necrosis in 11 patients, of whom two had necrosis of the transverse colon, and large pancreatic phlegmon in six.

Surgery was required in 11 patients; this included sump-catheter drainage in six and debridement of necrotic

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peripancreatic tissue in five. Operations were performed a median of 8 (range 1–32) days after admission. Nine patients in this group died from uncontrollable sepsis in spite of multiple laparotomies (mean 2·2 per patient). Two deaths from multiple organ failure occurred before intended surgery; both patients had pancreatic phlegmons confirmed on CT.

The patients with severe pancreatitis were significantly more obese than those with mild disease (mean(s.d.) BMI 31·2(5·6) *versus* 23·3(5·6) kg/m^2; $t = 5·42$, 97 d.f., $P < 0·001$) (*Figure 1*). The mortality rate of obese patients (seven of 19) was significantly higher than that in the other groups combined (four of 80) ($P = 0·0007$).

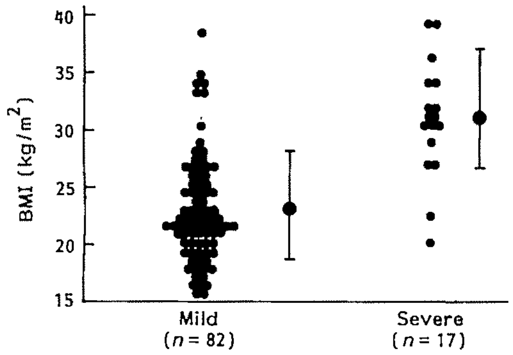

Figure 1 *Body mass index (BMI) according to severity of pancreatitis. Bars are mean(s.d.)*

Effect of body mass index on outcome

The association between BMI and outcome is summarized in *Table 1*. Most of the patients in the four categories were correctly assessed by simple clinical observation, although eight of the 17 with BMI 26–29 kg/m^2 were thought clinically to be obese. Complications in the underweight group comprising 14 men and one woman were rare: there was one pseudocyst but no other complications or deaths. In patients of normal weight, comprising 34 men and 14 women, complications occurred in two men with severe alcohol-induced pancreatitis (one infected pancreatic necrosis, one infected pseudocyst) and both died from multiple organ failure. Three of the 17 patients with BMI 26–29 kg/m^2 had severe pancreatitis and two died from infected pancreatic necrosis. All three were assessed as clinically obese.

The outcome in relation to age and aetiology is summarized in *Tables 2* and *3*. All eight obese alcoholic men developed severe pancreatitis and four died, compared with four severe attacks with three deaths among 64 non-obese alcoholic patients. None of the 14 patients (five obese, nine not) with gallstone pancreatitis developed complications or died. Of the remaining four deaths, three occurred in obese women: one after cholecystectomy, one idiopathic and one with *Ascaris*-induced pancreatitis. The remaining death was in an overweight woman with hyperlipidaemic pancreatitis.

Obesity and the Imrie scoring system

The validity of the Imrie multiple-factor scoring system in predicting severity (three or more positive criteria within 48 h of admission) was confirmed in the present patients. Fifteen of the 17 patients with severe pancreatitis had a positive Imrie

Table 1 *Association between body mass index, sex, age and complications in 99 patients*

Cohort	BMI (kg/m^2)	No.	Sex ratio (M:F)	Mean age (years)	Pancreatic		Imrie score ≥3	Severe disease	Death
					Phlegmon	Necrosis			
Underweight	<19	15	14:1	35	0	0	1	0	0
Normal	19–25	48	34:14	40	0	2*	3	2	2
Overweight	26–29	17	11:6	45	1	2	5	3	2
Obese	≥30	19	9:10	46	5	7	11	12	7

BMI, body mass index. *One necrosis and one infected pseudocyst

Table 2 *Aetiological factors and outcome for 80 patients of the non-obese group*

Aetiological factor	No.	Sex ratio (M:F)	Mean age (years)	Pancreatic		Severe disease	Death
				Phlegmon	Necrosis		
Alcohol	64	53:11	39	1	3	4	3
Gallstones	9	4:5	52	0	0	0	0
Ascaris	2	1:1	29	0	0	0	0
Hyperlipidaemia	1	0:1	33	0	1	1	1
Idiopathic	4	1:3	32	0	0	0	0

Table 3 *Aetiological factors and outcome for 19 patients of the obese group*

Aetiological factor	No.	Sex ratio (M:F)	Mean age (years)	Pancreatic		Severe disease	Death
				Phlegmon	Necrosis		
Alcohol	8	8:0	43	5	3	8	4
Gallstones	5	0:5	51	0	0	0	0
Ascaris	2	0:2	44	0	1	1	1
Postoperative	1	0:1	53	0	0	1	1
Idiopathic	3	1:2	42	0	2	2	1

score, as did five of the 82 with mild disease, a sensitivity of 88 per cent and specificity of 94 per cent. On the other hand, severe pancreatitis was recorded in 12 of the 19 obese patients and in five of 80 who were not obese, a sensitivity of 63 per cent and specificity of 95 per cent. When five obese women with gallstone pancreatitis were excluded, the sensitivity and specificity for obesity were 86 and 93 per cent respectively.

Discussion

This study supports the impression that obese patients (BMI ≥ 30 kg/m^2) are at increased risk of pancreatic necrosis, sepsis, systemic complications and death. No fewer than 12 of 19 such patients had severe pancreatitis and seven died. Overall, the mortality rate in obese patients was significantly higher than in the other weight groups combined.

The incidence of local complications, particularly infected pancreatic necrosis, was significantly higher in obese patients, with a similar trend being present in overweight individuals. This suggests that a greater volume of retroperitoneal fat may be an important factor that increases its susceptibility to necrosis and subsequent secondary infection with the formation of abscesses[10]. Retroperitoneal and intra-abdominal fat volume can be accurately determined using CT[11], but the technique is not reliable in the presence of pancreatic and peripancreatic inflammation. It is apparent from the present data, however, that an association exists between obesity and local peripancreatic complications.

In two previous studies[3,4] an increased incidence of systemic but not local complications was noted in obese patients. The present study, however, differs in patient material and, in particular, aetiological breakdown with respect to the Lankisch report[3]. The incidence of gallstone pancreatitis (30 per cent) in the latter study is higher than that of the present (14 per cent), whereas the figures for alcoholic pancreatitis are 33 and 72 per cent respectively. These differences may explain the disparity in complication rates, as aetiological factors appear to influence outcome. All five obese patients with gallstone pancreatitis in the present study had mild attacks, while severe pancreatitis occurred in 12 of the remaining 14 obese patients. All eight obese patients with an alcoholic aetiology and four of the six with disease from other causes had severe pancreatitis, with seven deaths. Larger studies are needed to assess the apparent better prognosis in obese patients with gallstone pancreatitis.

The early identification and prediction of patients at risk for severe pancreatitis has been intensively studied. Although a high level of accuracy has been achieved by the multiple-factor scoring systems of Ranson[12] and Imrie[9], and the APACHE II system[13], these complex schemes often attain a predictive value only after the severity of the attack is clinically obvious. Body-weight and height are simple reproducible measurements that can easily be made at the initial examination. Experience suggests that clinical assessment is sufficient to identify correctly the majority of obese patients. In the present study this single clinical observation had a high specificity and sensitivity, and can therefore be used as a reliable risk factor in the selection of patients requiring monitoring in an intensive care unit.

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References

1. Leger L, Chiche B, Louvel A. Pancreatic necrosis and acute pancreatitis. *World J Surg* 1981; **5**: 315–17.
2. Nordback I, Pessi T, Auvinen O, Autio V. Determination of necrosis in necrotising pancreatitis. *Br J Surg* 1985; **72**: 225–7.
3. Lankisch PG, Schirren CA. Increased body weight as a prognostic parameter for complications in the course of acute pancreatitis. *Pancreas* 1990; **5**: 626–9.
4. Porter KA, Banks PA. Obesity as a predictor of severity in acute pancreatitis. *Int J Pancreatol* 1991; **10**: 247–52.
5. Imrie CW, Whyte AS. A prospective study of acute pancreatitis. *Br J Surg* 1975; **62**: 490–4.
6. Keys A, Fidanza F, Karvonen MJ *et al.* Indices of relative weight and obesity. *Journal of Chronic Diseases* 1972; **25**: 329–43.
7. Roche AF, Siervogel RM, Chumlea WC. Grading of body fatness from limited anthropometric data. *Am J Clin Nutr* 1981; **34**: 2831–8.
8. Lew EA, Garfinkel L. Variations in mortality by weight among 750 000 men and women. *Journal of Chronic Diseases* 1979; **32**: 563–76.
9. Osborne DH, Imrie CW, Carter DC. Biliary surgery in the same admission for gallstone-associated pancreatitis. *Br J Surg* 1981; **68**: 758–61.
10. Beger HG, Bittner R, Block S, Büchler M. Bacterial contamination of pancreatic necrosis: a prospective clinical study. *Gastroenterology* 1986; **91**: 433–8.
11. Baumgartner RN, Heymsfield SB, Roche AF *et al.* Abdominal composition quantified by computed tomography. *Am J Clin Nutr* 1988; **48**: 936–45.
12. Ranson JHC, Rifkind KM, Roses DF *et al.* Prognostic signs and the role of operative management in acute pancreatitis. *Surg Gynecol Obstet* 1974; **139**: 69–81.
13. Larvin M, McMahon MJ. APACHE II score for assessment and monitoring of acute pancreatitis. *Lancet* 1989; **ii**: 201–4.

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Hereditary calcific pancreatitis in an English family

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Since the first published case[1] of a family with chronic calcific pancreatitis in 1952 approximately 25 other families have been documented in the world literature. The largest affected family to date included ten definite cases of pancreatitis and another four suspected[2]. This is the second documented English family.

The optimal surgical treatment is disputed. A family with five known affected members is presented (*Figure 1*), two of whom were successfully treated by distal pancreatectomy.

Case reports

Patient 1

The propositus, a woman aged 34 years, presented with severe epigastric pain associated with mildly raised serum amylase levels. From the age of 10 years she had had many episodes of central abdominal pain requiring several admissions to hospital without a firm diagnosis being made. Abdominal radiography showed calcification in the region of the pancreas. Computed tomography (CT) revealed extensive calcification throughout the gland with little remaining parenchyma. Endoscopic retrograde cholangiopancreatography showed dilated pancreatic ducts with multiple extraductal and intraductal calcifications. The patient was treated conservatively with analgesia, but the pain became intolerable, necessitating increasingly higher doses of opiates, and she developed steatorrhoea. At 3 years after initial presentation the patient underwent distal pancreatectomy with distal end-to-side pancreatojejunostomy and jejunojejunostomy. Histological analysis showed fibrosis and atrophy of acinar tissue consistent with non-specific pancreatitis. She has remained pain-free since the operation 7 years ago and the condition is well controlled by insulin and pancreatic enzyme supplements.

Patient 2

The eldest son of the propositus had suffered from epigastric pain since the age of 24 years. Abdominal radiography and CT confirmed the suspicion of calcific pancreatitis. He was initially treated with enzyme supplements and mild opiates, but symptoms persisted and worsened. At 6 months after presentation the patient underwent distal pancreatectomy and splenectomy with distal pancreatojejunostomy and jejunojejunostomy loop. Specimen radiography showed the extent of the disease (*Figure 2*). The postoperative course was uneventful, and 2 years later the man is pain-free with normal blood sugar levels.

Patient 3

The eldest daughter of the propositus presented at the age of 24 years with calcific pancreatitis (confirmed by radiography and CT) and diabetes. Initially the disease was well controlled by mild opiates; however, symptoms progressed and the patient has recently undergone distal pancreatectomy, 2 years after initial presentation.

Patient 4

The second youngest son of the propositus recently developed epigastric abdominal pain at the age of 16 years that occurs episodically and is associated with watery diarrhoea. Abdominal radiography showed no calcification in the pancreas although he had a raised serum amylase level of 400 units/l.

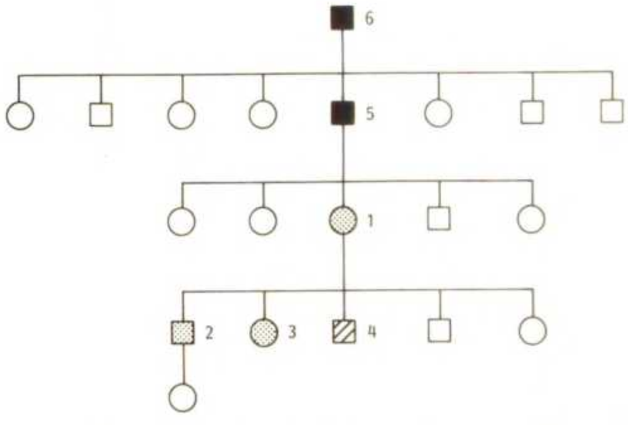

Figure 1 *Family tree.* ○, *Female;* □, *male;* ▨, *pancreatitis;* ■, *pancreatitis and pancreatic cancer;* ▧, *possible early pancreatitis*

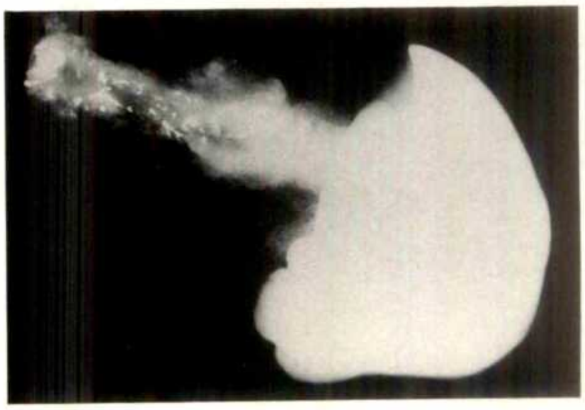

Figure 2 *Specimen radiograph following distal pancreatectomy in patient 2, demonstrating extensive pancreatic calcification extending to the hilum of the spleen*

Patient 5

The father of the propositus had a diagnosis of chronic calcific pancreatitis made at the age of 40 years, having suffered from abdominal pain since early adult life. He developed diabetes mellitus at 47 years and finally cancer of the pancreas at the age of 57 years. He died the following year.

Patient 6

The grandfather of the propositus had a similar history to that of her father. First, he developed chronic pancreatitis in his twenties and then cancer of the pancreas, from which he died at the age of 52 years.

Discussion

This family shows the typical features of hereditary calcific pancreatitis. It can be assumed that the disease was passed on from the grandfather of the propositus, indicating an autosomal dominant inheritance. In this family there appears to be a high level of gene penetration. This family demonstrates the unrelentingly progressive aspect of the disease and the high incidence of malignant change.

Previously the condition has been linked with a 25 per cent incidence of cancer of the pancreas[3]; there have been two cases so far in the present family. The other members of the family are being followed carefully as a result.

The treatment of patients with this disease is often unsuccessful. Conservative therapy usually offers only temporary relief and requires increasing doses of opiate analgesics. Surgical therapy has included drainage procedures with various degrees of success[4,5]. Total pancreatectomy has also been advocated, having a better chance of success in treating the intractable pain associated with the condition, although this operation

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carries a high degree of morbidity. Distal or subtotal pancreatectomy has also had mixed results, although patients 1 and 2 in this family experienced complete relief of pain after operation. While not advocating distal pancreatectomy for all patients, it is proposed that the procedure be considered when conservative therapy is failing.

References

1. Comfort MW, Steinberg AG. Pedigree of a family with hereditary chronic relapsing pancreatitis. *Gastroenterology* 1952; **21**: 54–63.
2. Dalton-Clarke HJ, Lewis MH, Levi AJ, Blumgart LH. Familial chronic calcific pancreatitis: a family study. *Br J Surg* 1985; **72**: 307–8.
3. Leger L, Soprani A, Bouvresse M, Liguory C. Pancreatite chronique familiale. *J Chir (Paris)* 1975; **110**: 519–32.
4. Gross JB, Comfort JW. Hereditary pancreatitis. Report on two additional families. *Gastroenterology* 1957; **32**: 829–54.
5. Davidson P, Costanza D, Swieconek JA, Harris JB. Hereditary pancreatitis; a kindred without gross aminoaciduria. *Ann Intern Med* 1968; **1**: 88–96.

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Intraluminal duodenal diverticulum: an unusual cause of acute pancreatitis

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Standard surgical texts list several rare causes of acute pancreatitis that should be considered when gallstones and alcohol have been excluded. This list should now also include intraluminal duodenal diverticulum, a congenital abnormality first described by Boyd[1] in 1845.

Case report

A 27-year-old woman was admitted to hospital with acute pancreatitis. During the preceding 7 months she had experienced several less severe episodes of epigastric pain. She did not drink alcohol, had normal serum lipid levels and a normal abdominal ultrasonography scan. Symptoms settled with conservative treatment. Some 2 months later she was readmitted after a more severe attack. Endoscopic retrograde cholangiopancreatography (ERCP) during this admission appeared to show a large polyp in the second part of the duodenum that obscured the papilla, preventing cannulation of the ampulla of Vater. A subsequent duodenogram supported the endoscopic findings (*Figure 1*).

At laparotomy 3 weeks later the duodenum was palpably normal but duodenotomy revealed a 7 × 2 cm duodenal diverticulum resembling a 'windsock' and which could be completely invaginated. The neck of the diverticulum was attached to 120° of the circumference of the duodenal wall at the level of the papilla and on the same side of the duodenum. Although the diverticulum was not causing luminal obstruction, when it was collapsed its free edge lay directly over the papilla. The diverticulum was excised along its mural attachment. Microscopically it comprised two layers of duodenal mucosa separated by muscularis mucosa. The patient made an uneventful recovery and after 6 months remains asymptomatic.

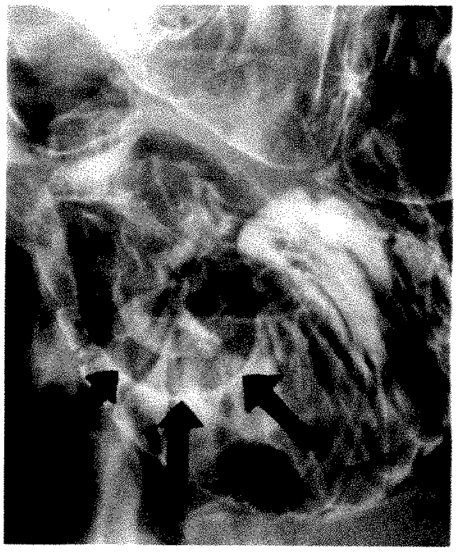

Figure 1 *Barium contrast study of the duodenum showing a large filling defect within the lumen (arrows) that was thought to be a polyp, although the screening radiologist noted that it appeared to change size and shape on different views*

Discussion

An intraluminal diverticulum, which is usually found in the second or occasionally the third part of the duodenum, is one of the least common forms of congenital duodenal abnormality. It occurs equally in both sexes. Approximately 50 cases have been reported in the world literature, 40 per cent of which have had coexistent anatomical abnormalities including choledochocele and annular pancreas[2]. In the 7-week-old normal embryo the duodenum becomes occluded and then recanalized. Incomplete recanalization causes either duodenal atresia, stenosis or a diaphragm[3]. A duodenal diverticulum, attached to all or part of the circumference of the duodenum, may be caused by ballooning of a diaphragm or may represent the remnant of dual recanalization, a theory postulated to explain its rare occurrence in neonates[4].

Intraluminal duodenal diverticula most commonly present in the third to fifth decades with abdominal pain and obstructive symptoms[5]. They have also been associated with gastrointestinal haemorrhage, although the exact site of bleeding is not always clear. The authors are aware of only ten cases in the literature of an intraluminal duodenal diverticulum causing pancreatitis[2]. Nance *et al.*[6] speculated that reflux of duodenal contents into the pancreatic duct might occur if the ampulla became deformed by filling of the diverticulum or if the duodenum became obstructed by the diverticulum. Alternatively, pancreatitis might result from obstruction to pancreatobiliary drainage caused by the diverticulum collapsing on to the papilla.

With the increasing use of ERCP for the investigation of pancreatitis, this abnormality may be encountered more frequently than before. Diverticulectomy, via a duodenotomy or endoscope, appears to be universally successful in preventing further attacks of pancreatitis.

References

1. Boyd R. Description of malformation of the duodenum. *Lancet* 1845; **i**: 648.
2. Adams DB. Management of the intraluminal duodenal diverticulum: endoscopy or duodenotomy. *Am J Surg* 1986; **151**: 524–6.
3. Krieg EG. Duodenal diverticulum. *Ann Surg* 1937; **106**: 33–41.
4. Heilbrun N, Boyden EA. Intraluminal duodenal diverticula. *Radiology* 1964; **82**: 887–94.
5. Fleming CR, Newcomer AD, Stephens DH, Carlson HC. Intraluminal duodenal diverticulum. Report of two cases and review of the literature. *Mayo Clin Proc* 1975; **50**: 245–8.
6. Nance FC, Cocchiara J, Kinder JL. Acute pancreatitis associated with an intraluminal duodenal diverticulum. *Gastroenterology* 1967; **52**: 544–7.

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Graft size assessment by preoperative computed tomography in living related partial liver transplantation

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The size of segmental liver grafts assessed by preoperative computed tomography (CT) volumetry was evaluated in relation to surgical outcome in 14 living related partial liver transplantations (LRLTs). The aim was to show that graft size can be accurately assessed before operation and to estimate the lower safety limit of graft size in assessing subsequent graft function and survival. The relationship between calculated CT volume and weight of the liver was linear in the recipient (r = 0·97) and donor (r = 0·98). The mean(s.e.m.) modified liver weight ratio (MLWR; ratio of graft weight to recipient's expected liver weight based on body-weight) was 0·59(0·07) (range 0·27–1·09). Surgical complications related to an oversized graft and primary graft failure caused by a small-for-size graft were not observed. The lowest MLWR of any survivor was 0·27. These results suggest that a partial liver graft reduced to about 30 per cent of the recipient's expected liver weight can tolerate LRLT well.

Recent advances in medical electronics have enabled hepatic volume determination *in vivo* by computed tomography (CT). This has made it possible to obtain accurate information on liver regeneration after hepatectomy[1] and about graft volume before transplantation[2–4]. In liver transplantation, a major concern for surgeons is the size of graft that is to fit into the recipient's abdominal cavity. Although the ideal size of the graft is that of the recipient's normal liver, the severe shortage of donor organs has compelled surgeons to accept size discrepancy. Therefore, more accurate assessment of graft size before operation and information on the possible limits of this size discrepancy would probably enlarge the pool of potential transplant recipients.

This institute initiated a series of living related partial liver transplantations (LRLTs) in June 1990 in the belief that it would allow surgeons to perform elective surgery with preoperative evaluation of immunological matching as well as liver volume determination and to use fresh grafts[3–6]. These merits would theoretically lead to improved results because the problems of rejection and primary non-functioning liver would be greatly reduced. Accurate assessment of graft size is essential before LRLT because a graft obtained from a living donor is usually taken from the left lateral or left lobe of the liver and is limited in size[3–6]. Even the use of the left lobe may result in hepatic failure in a large recipient, because of its small size compared with the minimum functional hepatic volume.

The aims of this study were to evaluate graft size assessed by CT in relation to surgical outcome in 14 LRLTs and to estimate a lower safety limit of partial liver graft volume that could tolerate the transplantation procedure and meet the recipient's metabolic needs.

Patients and methods

Patients

Between June 1990 and March 1991, 14 patients (six boys, eight girls) of mean age 4·4 years (range 8 months to 11 years) underwent LRLT for end-stage liver disease (*Table 1*). The series of LRLTs was approved by the ethics committee of Kyoto University. Partial hepatectomy in the living donors (12 mothers, two fathers; mean age 33·9 (range 24–40) years) was based on the segmental anatomy of the liver as applied to hepatic resection[7]. Seven children received Couinaud segments II and III (left lateral lobe), six segments II, III and IV (left lobe) and one segments V, VI, VII and VIII (right lobe) (*Table 1*). With the informed consent of parents, the 14 children and donors were evaluated for hepatic volume and size by CT before operation.

Liver computed tomography

CT of the liver for volume determination was performed using a Hitachi model CTW-1000 (Hitachi, Ibaragi, Japan). Serial transverse scans at 0·5-cm intervals from the dome of the liver to the most inferior part of the organ were obtained, with enhancement by an intravenous bolus injection of contrast medium. Using an electronic 'mouse' linked to a picture archival and communicating system[8], the perimeters of the left lateral, left and right lobes and of the whole liver were outlined on each slice and the enclosed area simultaneously calculated. The total volume of each lobe and of the whole liver was obtained by summing the volumes of individual slices. During hepatic volume determinations, the maximum anterior–posterior and left–right dimensions as well as axial length of the graft and recipient liver fossa were also measured.

Measurement of the weight of donor graft and recipient's liver

The weight of liver graft stored in University of Wisconsin solution was measured on a back-table. The weight of the recipient's liver containing blood was measured immediately after removal from the patient's abdominal cavity. The expected weight of the recipient's liver was calculated from the patient's ideal body-weight according to a previous report from Japan[9]. At the time of the calculation of ideal body-weight, allowance was made for ascites and/or pleural effusion.

Statistical analysis

Values are expressed as mean(s.e.m.). Differences were evaluated by Student's *t* test. Linear regression analysis was used to generate correlation equations. $P < 0·05$ was considered significant.

Results

Relationship between liver weight and liver volume determined by computed tomography

The mean(s.e.m.) hepatic volume calculated by the summation of areas technique using serial CT images was 613·5(114·3) (range 311–2034) cm^3 in the recipient and 227·7(30·2) (range 116–592) cm^3 in the donor. The mean(s.e.m.) weight of the same livers was 673·6(126·4) (range 250–2220) g in the recipient and 279·2(29·0) (range 174–630) g in the donor. The relationship between the calculated CT volume *in vivo* and the weight of the liver at operation was linear in the recipient

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Table 1 *Indications for partial liver transplantation from a living donor in 14 children*

Patient no.	Age (years)	Age (months)	Weight (kg)	Diagnosis	Indication	Body-weight ratio*	Hepatic segments implanted
1	9		17·8	Congenital biliary atresia	Elective	3·26	II, III, IV
2	3		14·0	Congenital biliary atresia	Elective	3·71	II, III, IV
3	9		24·2	Congenital biliary atresia	Elective	2·36	V, VI, VII, VIII
4	3		11·0	Budd–Chiari syndrome	Elective	5·32	II, III, IV
5	9		24·0	Cirrhosis	Deterioration, variceal bleeding	2·78	II, III, IV
6		11	9·0	Congenital biliary atresia	Deterioration, coma	5·00	II, III, IV
7	6		24·4	Congenital biliary atresia	Elective	2·19	II, III
8	11		36·8	Budd–Chiari syndrome	Deterioration	1·40	II, III, IV
9		15	8·1	Congenital biliary atresia	Elective	7·03	II, III
10		8	7·9	Congenital biliary atresia	Elective	6·80	II, III
11		8	7·2	Congenital biliary atresia	Elective	7·11	II, III
12		13	6·3	Congenital biliary atresia	Elective	7·41	II, III
13	5		16·8	Congenital biliary atresia	Elective	3·15	II, III
14	2		8·6	Congenital biliary atresia	Elective	7·23	II, III

*Body-weight of donor:body-weight of recipient

Table 2 *Size match between donor and recipient*

	Donor graft							
	Dimensions					Recipient liver fossa dimensions		
Transplantation no.	Anteroposterior (mm)	Left–right (mm)	Axial (mm)	Volume (cm³)*	Weight (g)†	Anteroposterior (mm)	Left–right (mm)	Axial (mm)
1	63	114	105	240	260	136	140	110
2	77	93	90	243	275	92	115	120
3	60	101	90	592	630	131	101	120
4	61	69	80	260	320	122	99	110
5	40	87	80	228	275	79	92	100
6	51	99	100	209	255	72	100	100
7	66	74	70	195	235	98	105	110
8	57	90	80	240	315	155	168	140
9	65	68	70	116	190	75	90	100
10‡	50	54	80	145	174	46	86	110
11	62	57	80	154	235	62	81	120
12	62	68	70	159	260	79	71	130
13	62	94	80	202	230	73	104	120
14	65	68	70	205	255	73	101	110

*Calculated from CT; †actual weight stored in University of Wisconsin solution; ‡anteroposterior fossa dimension in this recipient was less than that of the graft

($y = 1\cdot07x + 17$, $r = 0\cdot97$, $P < 0\cdot001$) and donor ($y = 0\cdot94x + 65$, $r = 0\cdot98$, $P < 0\cdot001$) (*Figure 1*).

Donor–recipient size match

Table 2 shows the anteroposterior, left–right and axial dimensions of the graft and recipient liver fossa. These three dimensions were always lower in grafts than those of the recipient liver fossa except for one case (LRLT 10), in which the anteroposterior dimension of the recipient was smaller than that of the graft. Despite this disparity of 4 mm, abdominal closure was performed without difficulty. No surgical complication related to an oversized graft was observed.

The ratio of graft weight to recipient's expected liver weight (modified liver weight ratio; MLWR) gradually decreased as the body-weight of the recipient increased, except in one case (LRLT 3) in which the patient received a right lobe as a graft (*Figure 2*). *Figure 3* shows the relationship between CT volume ratio (graft CT volume:recipient's liver CT volume) and MLWR. There was a significant difference between these two ratios. The lowest MLWR of any survivor was 0·27.

Graft function and survival

Changes in liver function test findings and arterial ketone body ratio, an accurate indicator of graft viability[10,11], before and after LRLT are given in *Table 3*. In all cases, the arterial ketone body ratio increased to > 1·0 by the second day after surgery. Two recipients, whose MLWR values were 0·31 and 0·30, died on days 25 and 21 after surgery respectively. The major causes of death were not, however, hepatic dysfunction but acute cardiac failure and renal failure due to the presence of cardiac dysfunction (patient 5) and renal damage with massive ascites (patient 8) before operation respectively. Another patient

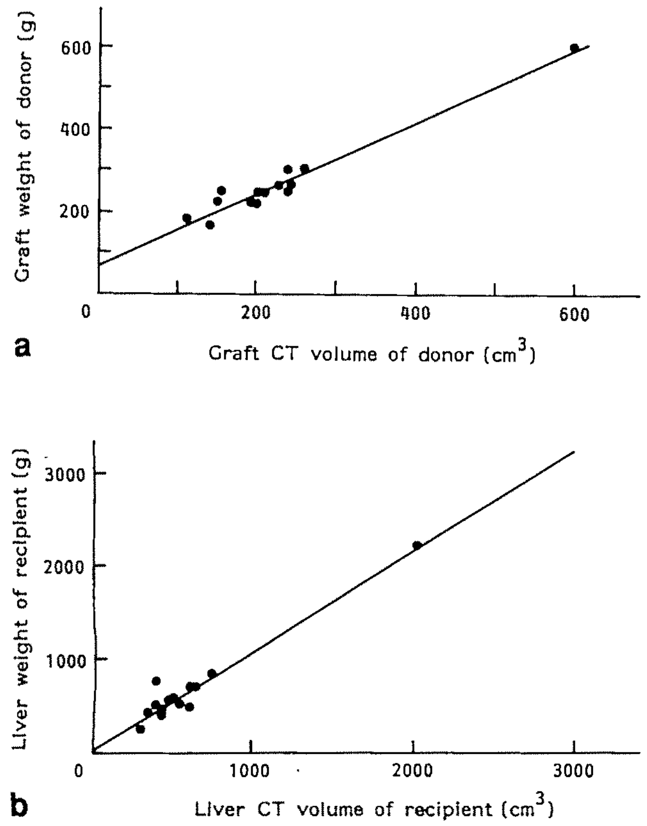

Figure 1 *Correlation between liver volume calculated from computed tomography (CT) and measured weight of the liver in* **a** *donors* (n = 14; $y = 0{\cdot}94x + 65$, $r = 0{\cdot}98$, $P < 0{\cdot}001$) *and* **b** *recipients* (n = 14; $y = 1{\cdot}07x + 17$, $r = 0{\cdot}97$, $P < 0{\cdot}001$)

(no. 1) died from accidental asphyxia on day 179 after surgery, about 5 months after discharge. The remaining 11 patients are alive and their grafts are functioning well, as shown by arterial ketone body ratio values >1·0 after a mean follow-up of 8·6 (range 4–14) months.

Discussion

These results demonstrate that an accurate determination of hepatic volume *in vivo* can be obtained by CT both in the whole liver of the recipient and in the segmental graft of the donor. Although determination of hepatic volume *in vivo* by CT has previously been documented by other investigators[2–4], an accurate assessment of a segmental graft before operation has yet to be reported. This information could easily be called up on the monitor for surgeons as they performed donor hepatectomy, using the 'mouse' linked to the communicating system.

An accurate assessment of hepatic segment size is of great importance in LRLT because it greatly influences the choice of segments to be used as a graft. In contast to others[3,4] who have avoided LRLT in recipients aged >2 years or with body-weight >15 kg, the age and weight ranges of the present children were 8 months to 11 years and 6–37 kg. From the viewpoint of size match, therefore, the concerns are not only that a segmental graft might be too large for abdominal closure in smaller recipients, but also that a graft might be too small to function well in larger recipients. The latter concern was one of the reasons for the decision to use the right lobe as a graft for patient 3.

Concerning the reduction of the liver to appropriate size, Otte *et al.* reported 54 reduced-size transplants in which a decision was made according to visual comparison of the size

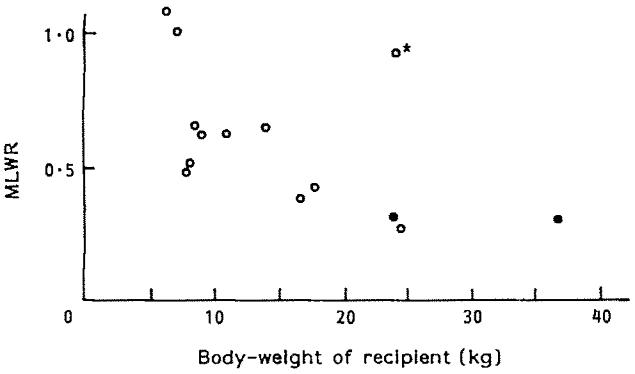

Figure 2 *Relationship between modified liver weight ratio (MLWR; ratio of graft weight to recipient's expected liver weight based on body-weight) and recipient body-weight.* * *Right lobe donation;* ●, *hospital death;* ○, *survivor*

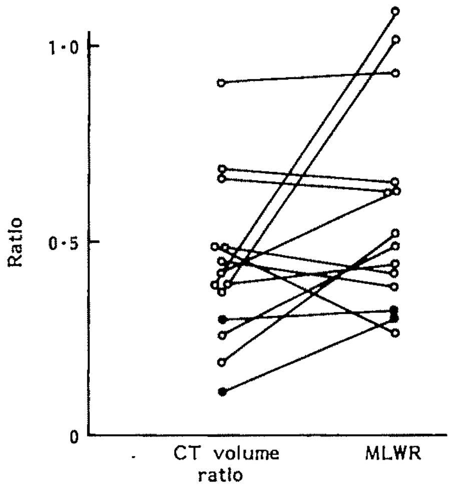

Figure 3 *Relationship between computed tomography (CT) volume ratio (graft CT volume:recipient's liver CT volume) and modified liver weight ratio (MLWR; ratio of graft weight to recipient's expected liver weight based on body-weight).* ●, *Hospital death;* ○, *survivor*

Table 3 *Results of hepatic function tests in recipients*

	SGOT (units/l)	SGPT (units/l)	LDH (units/l)	Total bilirubin (mg/dl)	AKBR
Before operation	182(31)	116(26)	511(41)	15·7(3·7)	0·43(0·19)
Time after operation					
6 h	—	—	—	—	0·99(0·17)
1 day	193(28)	166(32)	590(75)	6·1(1·3)	1·15(0·07)
2 days	145(20)	154(25)	670(67)	6·5(1·6)	1·56(0·14)

Values are mean(s.e.m.). SGOT, serum glutamic–oxaloacetic transaminase; SGPT, serum glutamic–pyruvic transaminase; LDH, lactic dehydrogenase; AKBR, arterial ketone body ratio and shape of the donor and recipient livers[12]. Broelsch *et al.* reported that the size reduction of the graft was performed according to the body-weight ratio between donor and recipient[3] or the ratio of the graft volume to recipient's body-weight[4]. This body-weight ratio is widely used to determine the extent of graft reduction[3,12,13]. However, the size and shape of the liver are not predictably related to body-weight, size and abdominal circumference. Moreover, the relative size and shape of the hepatic segments vary greatly in relation to the overall size of the organ. When a small-for-size liver is to be transplanted into a large recipient, we recommend that an accurate assessment of the graft size be carried out; the decision on which hepatic segments to use as a graft should be made with careful consideration of the recipient's expected ideal liver weight[14,15].

The weight of severely damaged liver in the recipient will differ from that of the normal liver because of the pathological condition and malnutrition. The present study therefore adopted the MLWR instead of the CT volume ratio and liver weight:body-weight ratio. This is why CT volume ratios of several patients showed different values from the MLWRs, although an accurate assessment of hepatic segment size was performed by CT.

The human liver can tolerate >70 per cent hepatectomy in the absence of cirrhosis[16]. It is, therefore, likely that a fresh graft of MLWR >0·30 could overcome the metabolic load of the recipient even if impaired by the transplantation procedures such as cold preservation, ischaemia time and reperfusion injury. In fact, in the present series no primary graft failure occurred as long as the MLWR was >0·27. However, the use of a fresh graft and the reduced mean(s.e.m.) anhepatic time (115·1(13·4) min) as well as the shorter preservation time (88·5(12·6) min) in LRLT may also have contributed to the good results. In liver transplantation from a cadaveric donor, the minimum small-for-size liver successfully transplanted in a large host is, to the present authors' knowledge, 41 per cent of the normal liver weight of a healthy individual of the same size, age and sex as the recipient[15]. Therefore, it seems likely that this lower limit of MLWR could be applied to widen the pool of potential transplant recipients if a well functioning good graft is obtained from cadaveric donors. In addition, knowledge of the lower safe limit of the MLWR is important for surgeons confronted with LRLT for adults. Using this knowledge, the left lateral segment could be used as a graft in the latter half of the present 14 LRLTs even when the body-weight ratio was approximately 2·0, since the donor hepatectomy had to be performed as safely as possible.

It is suggested that a living related segmental graft is safe if the ratio of the graft weight to the recipient's expected liver weight is >0·27 and that this ratio could, to some extent, be predicted by CT volume ratio before operation, when the recipient's liver weight can be calculated from ideal body-weight.

Acknowledgements

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References

1. Chen MF, Hwang TL, Hung CF. Human liver regeneration after major hepatectomy. *Ann Surg* 1991; **213**: 227–9.
2. Van Thiel DH, Hagler NG, Schade RR *et al. In vivo* hepatic volume determination using sonography and computed tomography. *Gastroenterology* 1985; **88**: 1812–17.
3. Broelsch CE, Emond JC, Whitington PF, Thistlethwaite JR, Baker AL, Lichtor JL. Application of reduced-size liver transplants as split grafts, auxiliary orthotopic grafts, and living related segmental transplants. *Ann Surg* 1990; **212**: 368–77.
4. Broelsch CE, Whitington PF, Emond JC *et al.* Liver transplantation in children from living related donors. *Ann Surg* 1991; **214**: 428–39.
5. Raia S, Nery JR, Mies S. Liver transplantation from live donors. *Lancet* 1989; **ii**: 497.
6. Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful liver transplantation from a living donor to her son. *N Engl J Med* 1990; **322**: 1505–7.
7. Yamaoka Y, Ozawa K, Tanaka A *et al.* New devices for harvesting hepatic graft from the living donor. *Transplantation* 1991; **52**: 157–60.
8. Komori M, Minato K, Nakano Y *et al.* Pilot PACS with on-line communication between an image workstation and CT scanners in a clinical environment. *Proceedings of the International Society for Optical Engineering* 1987; **767**: 744–67.
9. Aimi S, Yasoshima S, Sugai M, Sato B, Sakai T, Nakajima Y. Studies on the weight and size of internal organs of normal Japanese. *Acta Pathol Jpn* 1952; **2**: 173–200.
10. Asonuma K, Takaya S, Selby R *et al.* Clinical significance of the arterial ketone body ratio as an early indicator of graft viability in human liver transplantation. *Transplantation* 1991; **51**: 164–71.
11. Ozaki N, Ringe B, Bunzendahl H *et al.* Ketone body ratio as an indicator of early graft survival in clinical liver transplantation. *Clin Transpl* 1991; **5**: 48–54.
12. Otte JB, de Ville de Goyot J, Sokal E *et al.* Size reduction of the donor liver is a safe way to alleviate the shortage of size-matched organs in pediatric liver transplantation. *Ann Surg* 1990; **211**: 146–57.
13. Kalayoglu M, D'Alessandro AM, Sollinger HW, Hoffman RM, Pirsch JD, Belzer FO. Experience with reduced-size liver transplantation. *Surg Gynecol Obstet* 1990; **171**: 139–47.
14. Kam I, Lynch S, Svanas G *et al.* Evidence that host size determines liver size: studies in dogs receiving orthotopic liver transplants. *Hepatology* 1987; **7**: 362–6.
15. Van Thiel DH, Gavaler JS, Kam I *et al.* Rapid growth of an intact human liver transplanted into a recipient larger than the donor. *Gastroenterology* 1987; **93**: 1414–19.
16. Stone HH, Long WD, Smith RB III, Haynes CD. Physiological considerations in major hepatic resection. *Am J Surg* 1969; **117**: 78–84.

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Ultrasonography during liver resection for hepatocellular carcinoma

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Seventy-nine consecutive patients underwent elective laparotomy for symptomatic hepatocellular carcinoma between 1986 and 1992. In the first 4 years, 51 patients received liver resection without intraoperative ultrasonography. In the subsequent 2 years, ultrasonography was performed during operation on 28 patients; three were found to have inoperable tumours. The technique located tumours in two patients and changed the extent of liver resection in another two. Eight of 51 patients (16 per cent) who had the parenchymal transection plane determined clinically had histological evidence of tumour infiltration of the resection margins, compared with none of 25 in whom the plane was determined by ultrasonography. This difference was significant (P = 0·034). *The use of intraoperative ultrasonography improved patient survival, although this was not statistically significant. The median survival of patients with adequate resection margins was 9·2 months, compared with 3·9 months in those with inadequate margins. Intraoperative ultrasonography is useful in surgery for hepatocellular carcinoma.*

Intraoperative ultrasonography is now used routinely in many centres. Hepatocellular carcinoma (HCC) complicating cirrhosis is one indication for use of this technique. The search for a small neoplastic nodule within the firm nodular cirrhotic liver can be difficult and such non-palpable lesions can often be located only by intraoperative ultrasonography. Preservation of functioning liver tissue is an important surgical goal. Ultrasonography clearly displays the extent of the tumour, its relationship with the hepatic vascular anatomy, and the potential resection plane. This information is obtained at the outset of surgery, so that exploratory tissue dissection and irreversible surgical manoeuvres can be avoided in patients with irresectable tumours. An adequate resection margin can be planned for those with operable lesions.

At this hospital intraoperative ultrasonography has been used routinely for the past 2 years in all patients undergoing liver resection for HCC. Its impact on decision making during operation, on the incidence of positive liver resection margins and on patient survival are the subject of this study.

Patients and methods

Between January 1986 and February 1992, 79 consecutive patients underwent elective surgery with curative intent for symptomatic HCC.

A detailed history was obtained from all new patients. Laboratory and radiological investigations included full blood count, estimation of blood glucose level, liver profile, liver enzyme assays, prothrombin and partial prothrombin times, hepatitis B surface antigen and α-fetoprotein determinations, chest radiography and hepatic ultrasonography. Patients who were reasonably fit and deemed to have resectable tumours on ultrasonography underwent further investigation by computed tomography (CT) and selective hepatic angiography. Hepatic intra-arterial injection of Lipiodol (May and Baker, Guerbet, Zurich) combined with CT and ultrasonography were carried out only when clinically indicated. The tumour was considered to be inoperable when there was extrahepatic spread, main portal vein invasion or extensive bilobar disease.

Laparotomy was performed through a bilateral subcostal incision. Before the availability of intraoperative ultrasonography, the liver was examined and the line of parenchymal transection determined by gross examination. Since 1990 this has been carried out using ultrasonography equipment (Aloka SSD-650; Aloka, Tokyo, Japan). A resection margin 2 cm from the edge of the tumour, determined clinically or ultrasonographically, was used. The line of intended liver parenchyma transection was marked on the liver surface using diathermy.

In anatomical resections, preliminary hilar ligation of the branches of the hepatic artery and portal vein supplying the segments to be resected was carried out. This step was omitted in non-anatomical resections. The hepatic veins were secured outside when convenient, or inside the parenchyma when the liver was transected. Liver transection was carried out by finger fracture, ultrasonic dissection or microwave tissue coagulation[1].

The resected specimens were studied for neoplastic infiltration at the parenchymal transection plane. All patients were followed regularly at intervals of 4–12 weeks. Blood was taken for estimation of α-fetoprotein level and ultrasonography of the liver carried out every 3 months in the first year after operation and thereafter at longer intervals to detect tumour recurrence.

Results

Of the 79 patients, 76 underwent liver resection with curative intent; 51 had no intraoperative ultrasonography compared with 25 who did. The demographic data of these two patient groups were comparable. More patients underwent minor liver resection (segmentectomy and non-anatomical procedures) in the group that had ultrasonography (44 per cent) than in the group that did not (26 per cent).

Ultrasonography showed that three patients had inoperable tumours despite extensive preoperative investigation. Two had widely disseminated secondary deposits proven with biopsy and the third had a tumour thrombus in the right hepatic vein eroding into the inferior vena cava. In two patients undergoing intraoperative ultrasonography, another secondary deposit was detected that was judged to be resectable by extending the original plane of resection, as the nodules were adjacent to the primary tumours. In another two patients, the tumours could not be seen or felt and were successfully located by ultrasonography. Intraoperative ultrasonography helped significantly in making the surgical decision in seven of 28 patients (25 per cent).

Eight of the 51 patients (16 per cent) in whom the plane of liver parenchyma transection was determined by gross examination had histological evidence of neoplastic infiltration of the resection margins compared with none of the 25 who had the plane determined by intraoperative ultrasonography. The difference between the two groups was statistically significant ($P = 0{\cdot}034$, Fisher's exact test).

Patients who underwent intraoperative ultrasonography

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had a better survival rate than those who did not, although the difference between the two survival curves was not significant ($P = 0{\cdot}44$, log rank test). The median survival for patients with negative resection margins was 9·2 months compared with 3·9 months for those with positive margins. There was no significant difference between the two survival curves ($P = 0{\cdot}32$, log rank test).

Discussion

Intraoperative ultrasonography 'extends' the eyes and hands of the surgeon[2], permits the discovery of tumours overlooked during preoperative examination, allows mapping of lesions, defines the extent of disease, and determines the relationship to, and involvement of, vascular structures[2–14].

The advantages of intraoperative ultrasonography are notable in patients with cirrhosis, in whom surgical examination is difficult and parenchymal tumours cannot be felt because of the firm consistency of the liver. Nagasue *et al.* found that approximately half of tumours <4 cm in diameter in cirrhotic livers could not be palpated[8]. Sheu and colleagues reported that intraoperative ultrasonography was indispensible in >30 per cent of cases, enabling limited resection of small impalpable tumours in cirrhotic livers[9]. Intraoperative ultrasonography is three times as sensitive as preoperative examination in detecting tumour thrombus in the portal venous branches and hepatic veins[2]. Gozzetti *et al.* described 28 patients with cirrhosis, six of whom had satellite liver nodules (mean diameter 1·3 cm) not seen before operation or palpated during surgery; these patients did not undergo hepatic resection[7].

The incidence of involved resection margins is seldom reported in the literature. Lai *et al.* found that, even with macroscopic clearance, parenchymal infiltration or venous permeation at the line of parenchymal transection was detected histologically in 27·6 per cent of patients[15]. When lesions of all sizes were studied together, Lee *et al.* recommended a resection margin of 1 cm because a significantly better survival rate was found in patients with such an extent of tumour clearance[16]. Yoshida *et al.* suggested that a resection margin ≤1 cm is inadequate in preventing intrahepatic recurrence for tumours >4 cm in diameter[17]. A wide resection margin may achieve a high rate of complete extirpation of the disease but increases the risk of postoperative encephalopathy and hepatic failure in those with cirrhosis. In none of the studies cited above was intraoperative ultrasonography used to help determine the extent of resection. Ultrasonography allows better definition of margins, and the plane of liver transection can be orientated to avoid injury to the major portal or hepatic branches, thus preserving functioning liver parenchyma[2]. Intraoperative ultrasonography has been used to orientate the surgeon during hepatic parenchyma transection so as to obtain an adequate resection margin[12] and, because it delineates the relationship of the tumour to the vascular structures, a more limited resection is permitted[14]. This may explain why there were more patients with minor liver resection in the group undergoing ultrasonography. Intraoperative ultrasonography has facilitated the development of two new operative procedures: systemic subsegmentectomy[3] and inferior right hepatic vein-preserving hepatectomy[18].

After apparently successful hepatic resection, recurrence and metastasis are the most frequent causes of subsequent mortality[10]. These are the result of residual disease that remains because conventional examination fails to detect small satellite lesions or because the resection margin is inadequate. The improvement in patient survival in the present study may have resulted from an increase in surgical experience with hepatectomy, the introduction of other new techniques such as ultrasonic dissection, and the use of minor resection in a higher proportion of patients in whom intraoperative ultrasonography was employed. The results show that intraoperative ultrasonography is helpful in making decisions during surgery and reducing the incidence of histologically positive margins. Patient survival was improved after liver resection, although not significantly so. Tumour-free resection margins probably have a beneficial effect on survival. The effects may not have been significant because the number of patients studied was small, some died from disseminated disease (presumably because the tumour had already spread at the time of liver resection) and some of the tumour nodules in the liver were missed. A major difficulty in the cirrhotic liver is to differentiate regenerative nodules from small HCC. Despite its limitations, intraoperative ultrasonography contributes significantly to the management of patients with HCC and routine use of the technique is advocated.

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References

1. Lau WY, Arnold M, Guo SK, Li AKC. Microwave tissue coagulator in liver resection for cirrhotic patients. *Aust N Z J Surg* 1992; **62**: 576–81.
2. Deixonne B, Lopez FM. *Operative Ultrasonography.* Berlin: Springer-Verlag, 1988.
3. Makuuchi M, Hasegawa H, Yamazaki S. Ultrasonically guided subsegmentectomy. *Surg Gynecol Obstet* 1985; **161**: 346–50.
4. Traynor O, Castaing D, Bismuth H. Peroperative ultrasonography in the surgery of hepatic tumours. *Br J Surg* 1988; **75**: 197–202.
5. Gozzetti G, Mazziotti A, Bolondi L *et al.* Intraoperative ultrasonography in surgery for liver tumours. *Surgery* 1986; **99**: 523–9.
6. Igawa S, Sakai K, Kinoshita H, Hirohashi K. Intraoperative sonography: clinical usefulness in liver surgery. *Radiology* 1985; **156**: 473–7.
7. Gozzetti G, Mazziotti A, Bolondi L, Barbara L. *Intraoperative Ultrasonography in Hepato-biliary and Pancreatic Surgery.* Dordrecht: Kluwer Academic, 1989.
8. Nagasue N, Suehio S, Yakaya H. Intraoperative ultrasonography in the surgical treatment of hepatic tumours. *Acta Chirurgica Scandinavica* 1984; **150**: 311–16.
9. Sheu JC, Lee CS, Sung JL, Chen DS, Yang PM, Lin TY. Intraoperative hepatic ultrasonography. An indispensible procedure in resection of small hepatocellular carcinoma. *Surgery* 1985; **97**: 97–103.
10. Rifkin MD, Rosato RE, Branch HM *et al.* Intraoperative ultrasound of the liver. *Ann Surg* 1987; **205**: 466–72.
11. Bismuth H, Castaing D, Garden OJ. The use of operative ultrasound in surgery of primary liver tumors. *World J Surg* 1987; **11**: 610–14.
12. Makuuchi M, Hasegawa H, Yamazaki S *et al.* The use of operative ultrasound as an aid to liver resection in patients with hepatocellular carcinoma. *World J Surg* 1987; **11**: 615–21.
13. Clarke MP, Kane RA, Steele D. Prospective comparison of preoperative imaging and intraoperative ultrasonography in the detection of liver tumors. *Surgery* 1987; **101**: 678–84.
14. Parker GA, Lawrence W, Horsely S *et al.* Intraoperative ultrasound of the liver affects operative decision making. *Ann Surg* 1987; **209**: 569–77.
15. Lai ECS, Ng IOL, Ng MMT *et al.* Long term results of resection for large hepatocellular carcinoma: a multivariate analysis of clinicopathological features. *Hepatology* 1990; **11**: 815–18.
16. Lee CS, Sung JL, Hwang LY *et al.* Surgical treatment of 109 patients with symptomatic and asymptomatic hepatocellular carcinoma. *Surgery* 1986; **99**: 481–90.
17. Yoshida Y, Kanematsu T, Matsumata T, Takenaka K, Sugimachi K. Surgical margin and recurrence after resection of hepatocellular carcinoma in patients with cirrhosis: further evaluation of limited hepatic resection. *Ann Surg* 1989; **209**: 297–301.
18. Makuuchi M, Hasegawa H, Yamazaki S, Takayasu K. Four new hepatectomy procedures for resection of the right hepatic vein and preservation of the inferior right hepatic vein. *Surg Gynecol Obstet* 1987; **164**: 69–72.

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Changes in liver blood flow associated with the growth of hepatic LV10 and MC28 sarcomas in rats

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Abnormalities in liver blood flow are known to occur in patients and animals with overt hepatic tumour. This study investigated the changes in liver blood flow associated with the development of overt hepatic tumour in two different models. Hepatic tumour was induced by intraportal inoculation of either 300 LV10 sarcoma cells or 10^5 MC28 sarcoma cells in rats. Liver blood flow and hepatic haemodynamics were measured 3 weeks later when overt liver tumour was present. The hepatic perfusion index (HPI), the ratio of hepatic arterial to total liver blood flow, was raised and portal venous inflow reduced in rats with LV10 tumours, but not in those with MC28 lesions. Hepatic arterial flow was unchanged in LV10 tumours when the HPI was raised and neither model demonstrated arteriosystemic or portosystemic shunting. The changes in portal venous inflow were associated with a significant increase in portal and splanchnic vascular resistance. These studies suggest that liver blood flow changes in the presence of overt hepatic tumour are not related to portal venous obstruction but may be caused by a circulating splanchnic vasoconstrictor.

Abnormalities in liver blood flow are known to occur in patients with colorectal liver metastases. Leveson *et al.*[1] demonstrated that changes in hepatic haemodynamics associated with the development of colorectal secondaries could be identified using dynamic hepatic scintigraphy. The hepatic perfusion index (HPI), the ratio of hepatic arterial to total liver blood flow, was shown to be abnormally raised in patients with overt hepatic metastases. In addition, 96 per cent of a group of patients with an apparently normal liver at presentation but who developed clinically apparent metastases over the ensuing year had a raised HPI at presentation.

It has been observed in both hypovascular and hypervascular models of hepatic tumour in the rat that the HPI is similarly raised in the presence of both overt and micrometastatic liver tumour[2,3]. In these models of hepatic tumour induced by intraportal inoculation of either HSN sarcoma or Walker carcinosarcoma cells the changes in liver blood flow responsible for the raised HPI were caused primarily by a decrease in portal venous inflow[2]. Portal and splanchnic vascular resistance were also increased, suggesting that the reduction in portal venous inflow may be related to the presence of a circulating splanchnic vasoconstrictor and not secondary to the intrahepatic portal venous obstruction reported by some authors[3]. However, it is possible that not all liver tumour results in alterations in hepatic haemodynamics. Therefore, to determine whether such changes in blood flow are a feature of all liver tumours, the present investigation was undertaken in two further models of overt hepatic tumour in the rat. In addition, the low number of LV10 tumour cells inoculated effectively eliminates effects caused by the intraportal introduction of a large particulate bolus.

Materials and methods

Experimental tumours

Two tumour cell lines, LV10 and MC28 sarcomas, were used. LV10 is a variant of the HSN sarcoma that has been conditioned by sequential passage for growth in the liver of Hooded Lister rats and MC28 is a methylcholanthrene-induced sarcoma that also grows in the liver of such rats. Both cell lines were grown in Dulbecco's modified-Eagles medium supplemented with 10 per cent fetal calf serum, 10 mmol glutamine and penicillin–streptomycin solution. Cells were released with trypsin from a confluent monolayer; viability assessed by trypan blue exclusion was 95 per cent. Hepatic tumour was induced by the intraportal inoculation of a single cell suspension of either 300 LV10 or 10^5 MC28 cells in male Hooded Lister rats (weight 200–250 g).

Dynamic hepatic scintigraphy

It has previously been reported that all the parameters of hepatic haemodynamics and blood flow are unchanged after intraportal inoculation of dead tumour cells[2,4,5], thereby eliminating the effects of a previous laparotomy or the intraportal introduction of cellular material as contributory to any of the changes in liver blood flow associated with the development of hepatic tumour. Therefore, in this study, a series of normal uninoculated animals were used as controls.

Experiments were performed 3 weeks after the intraportal inoculation of tumour cells when overt tumour was present in the liver (LV10, $n = 7$; MC28, $n = 8$), or in uninoculated controls ($n = 10$). The technique for performing dynamic hepatic scintigraphy in the rat has previously been described in detail[2,4]. Briefly, after an overnight fast the animals were anaesthetized by intraperitoneal injection of sodium pentobarbitone (30 mg kg^{-1}). A cannula was screened into position in the outflow tract of the left ventricle via the right carotid artery and adequate expulsion of a bolus assessed by injection of a 0·1-ml bolus of sodium meglumine.

Dynamic hepatic scintigraphy was performed using a rapid intraventricular injection of 0·4 ml albumin colloid labelled with 80 MBq ^{99m}Tc. Images were obtained at a rate of 3 s^{-1} on a γ camera with a pinhole collimator and stored on hard disc for subsequent analysis. Regions of interest were drawn on a composite image to correspond with the left ventricle, right kidney and liver. Care was taken to exclude the upper pole of the right kidney, the lower border of the right lung and the aorta from the regions of interest. Time–activity curves were then generated from these regions of interest and subjected to a maximum of three quadratic smoothings. The gradients of the hepatic arterial and portal venous phases of the hepatic time–activity curves were calculated by linear regression analysis. Since the gradients of these two components of the time–activity curve are proportional to hepatic arterial and portal venous flow, the HPI was calculated as the ratio of the hepatic arterial gradient to the sum of the hepatic arterial and portal venous gradients.

Blood flow

Immediately after completion of dynamic hepatic scintigraphy, organ

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blood flow was determined using the reference microsphere technique[6]. In brief, a cannula was placed in the right femoral artery and the animals received an intraventricular injection of 10^5 ^{57}Co-labelled microspheres (Nentrak; Du Pont, Stevenage, UK) 15 μm in diameter, in 0·3 ml 0·9 per cent saline with 0·01 per cent Tween 20 (Sigma Chemicals, Poole, UK) over 20 s. The suspension was thoroughly mixed before injection to ensure disaggregation of the microspheres. A reference sample of blood was withdrawn from the femoral arterial cannula at a constant rate of 1 ml min^{-1} beginning 20 s before and continuing for 40 s after the end of microsphere injection. At 5 min the animals were killed, the organs removed and weighed, and the radioactivity in them counted on a well γ counter 1 week later when the ^{99m}Tc had decayed. Organ blood flow was calculated according to the method of McDevitt and Nies[6].

$$\text{Organ blood flow (ml min}^{-1}) = \frac{\text{organ radioactivity (c.p.m.)}}{\text{reference sample radioactivity (c.p.m.)}} \times \text{reference withdrawal rate (ml min}^{-1})$$

Results were rejected if there was a difference of >10 per cent between blood flow values to the two kidneys, indicating inadequate ventricular mixing of the microspheres, or if any sample contained fewer than 400 particles since this reduces the accuracy of the counting statistics[7]. Hepatic arterial flow was determined from the counts in the liver and portal venous inflow from counts in the splanchnic organs draining into the portal vein.

Hepatic tumours were carefully separated from the surrounding parenchyma, and both tumour and normal liver weighed to allow calculation of the percentage hepatic replacement by weight.

Haemodynamics

Two further groups of eight animals were inoculated with live LV10 or MC28 tumour cells. A group of uninoculated rats acted as controls. Intrahepatic arteriosystemic shunting was determined using consecutive injections of ^{99m}Tc-labelled methylene diphosphonate and ^{99m}Tc-labelled macroaggregated albumin microspheres (Pharmacia, Uppsala, Sweden) via a cannula placed in the gastroduodenal artery as described previously[2,4]. All the injected diphosphonate passes through the liver whereas the aggregated albumin is retained in normal hepatic parenchyma. Arteriosystemic shunting is expressed as the percentage of counts detected in the lungs after macroaggregated albumin injection compared with the counts detected after methylene diphosphonate injection. Portosystemic shunting was determined in a similar manner after injection of the isotopes into the portal vein.

Portal pressure was measured using a pressure transducer (Gould Medical, Lutterworth, UK) attached to a cannula in the portal vein, and systemic arterial pressure using a similar transducer attached to a cannula in the gastroduodenal artery. Measurement of portal venous flow was made by placing an electromagnetic flow probe around the mobilized portal vein cranial to the gastroduodenal vein. The flow probe was set on zero *in vivo* by occlusion of the portal vein distal to the probe and flow measured 30 s after release of the clamp. Portal and splanchnic vascular resistance were calculated in each rat as:

$$\text{Portal vascular resistance (mmHg ml}^{-1}\text{ min)} = \frac{\text{portal pressure (mmHg)}}{\text{measured portal flow (ml min}^{-1})}$$

$$\text{Splanchnic vascular resistance (mmHg ml}^{-1}\text{ min)} = \frac{\text{arterial pressure (mmHg)}}{\text{measured portal flow (ml min}^{-1})}$$

Statistical analysis

Comparison of each of the experimental groups with the controls was made using the Mann–Whitney *U* test.

Results

Dynamic hepatic scintigraphy

The median HPI in control animals was 32·5 (range 26–41). The median value in rats with overt LV10 tumour was 61·0 (range 47–79) ($P = 0·0008$). The median value for overt MC28 tumour, 40·0 (range 26–56), was not significantly different from that of controls (*Figure 1*).

Blood flow

Median (range) hepatic arterial flow in animals with LV10 tumour, 2·00 (0·44–3·69) ml min^{-1}, was not significantly different from that in uninoculated controls, 2·43 (0·70–4·43) ml min^{-1} ($P = 0·35$). Median hepatic arterial flow in rats with MC28 tumours, 3·63 (range 2·00–5·73) ml min^{-1}, was significantly greater than in controls ($P = 0·037$) (*Table 1*, *Figure 2*). Portal venous inflow in rats with overt LV10 tumours was significantly lower than in controls (median (range) 2·56

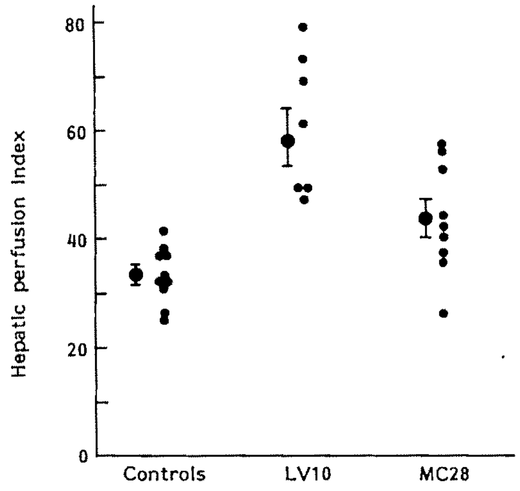

Figure 1 *Hepatic perfusion index in control rats and animals with hepatic LV10 and MC28 tumours. Bars are mean(s.e.m.)*

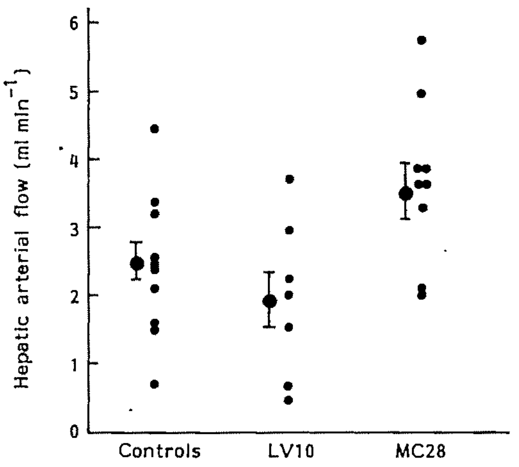

Figure 2 *Hepatic arterial flow in control rats and animals with hepatic LV10 and MC28 tumours. Bars are mean(s.e.m.)*

Table 1 *Hepatic arterial flow, portal venous inflow and portal pressure in rats with hepatic LV10 and MC28 tumours*

	Controls	LV10	MC28
Hepatic arterial flow (ml min^{-1})	2·43 (0·70–4·43)	2·00 (0·44–3·69)	3·63 (2·00–5·73)*
Portal venous inflow (ml min^{-1})	8·35 (2·22–16·01)	2·56 (1·05–9·22)†	6·86 (1·35–11·83)
Portal pressure (mmHg)	7·7 (4·7–12·0)	13·0 (3·4–16·5)	9·7 (5·6–14·5)

Values are median (range). *$P = 0·037$; †$P = 0·013$ (*versus* controls, Mann–Whitney *U* test)

(1·05–9·22) *versus* 8·35 (2·22–16·01) ml min^{-1}, $P = 0·013$). In contrast, median portal venous inflow in rats with MC28 tumours, 6·86 (range 1·35–11·83) ml min^{-1}, did not differ significantly from that in control animals (*Table 1, Figure 3*).

Haemodynamics

Portal pressure and flow. There were no significant differences in portal pressure between normal animals and those with LV10 or MC28 tumours (*Table 1*). Measured median (range) portal flow in control animals was significantly higher than in rats with LV10 tumours, 14·5 (10–20) *versus* 10·0 (8–13) ml min^{-1} ($P = 0·002$), and in animals with MC28 tumours, 10·0 (9–15) ml min^{-1} ($P = 0·0034$) (*Figure 4*).

Portal vascular resistance. The median (range) portal vascular resistance in rats with LV10 tumours was 0·99 (0·38–1·83) mmHg ml^{-1} min and for those with MC28 lesions 0·95 (0·47–1·45) mmHg ml^{-1} min, both of which were significantly greater than the value in control animals, 0·48 (0·33–0·92) mmHg ml^{-1} min (LV10, $P = 0·011$; MC28, $P = 0·024$) (*Table 2, Figure 5*).

Splanchnic vascular resistance. Median (range) splanchnic vascular resistance was 10·80 (6·36–20·0) mmHg ml^{-1} min in rats with LV10 tumours, which was significantly greater than the value in control animals, 7·00 (3·30–11·80) mmHg ml^{-1} min ($P = 0·024$), but splanchnic vascular resistance in rats with MC28 tumours, 7·15 (5·22–9·90) mmHg ml^{-1} min, was not significantly raised compared with that in control animals ($P = 0·62$) (*Table 2, Figure 6*).

Arteriosystemic and portosystemic shunting. There were no significant differences in arteriosystemic or portosystemic

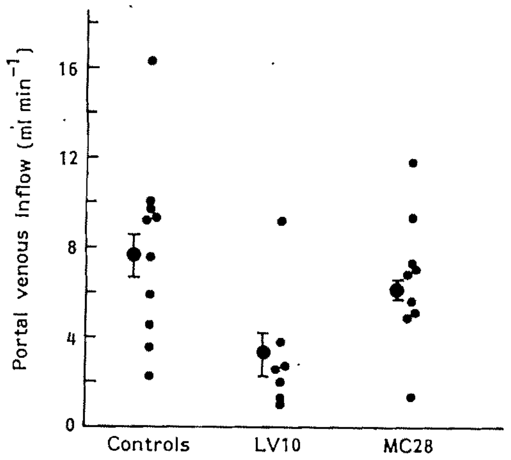

Figure 3 *Portal venous inflow in control rats and animals with hepatic LV10 and MC28 tumours. Bars are mean(s.e.m.)*

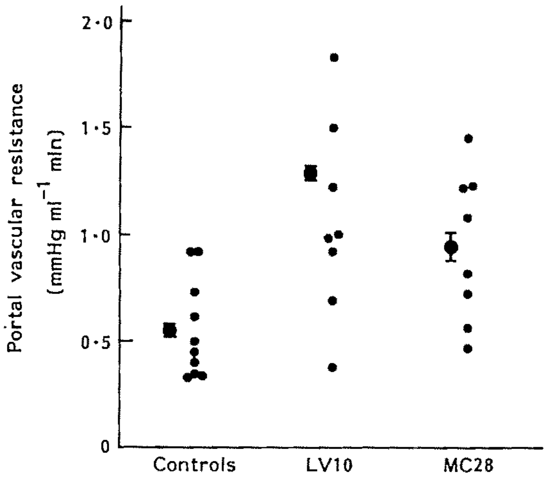

Figure 5 *Portal vascular resistance in control rats and animals with hepatic LV10 and MC28 tumours. Bars are mean(s.e.m.)*

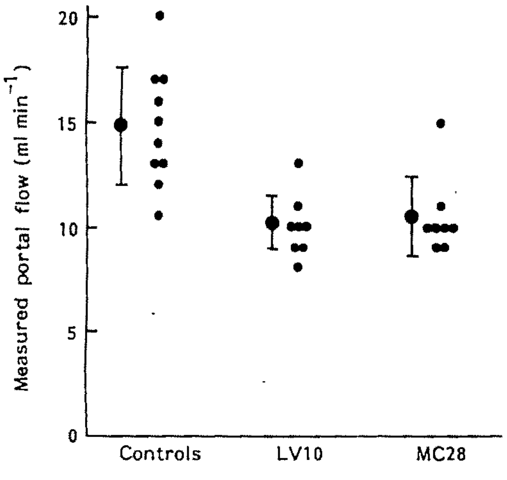

Figure 4 *Measured portal flow in control rats and animals with hepatic LV10 and MC28 tumours. Bars are mean(s.e.m.)*

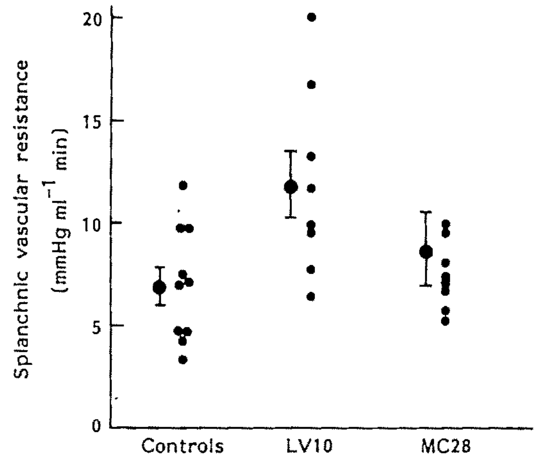

Figure 6 *Splanchnic vascular resistance in control rats and animals with hepatic LV10 and MC28 tumours. Bars are mean(s.e.m.)*

Table 2 *Portal and splanchnic vascular resistance in rats with hepatic LV10 and MC28 tumours*

	Controls	LV10	MC28
Portal vascular resistance (mmHg ml^{-1} min)	0·48 (0·33–0·92)	0·99 (0·38–1·83)*	0·95 (0·47–1·45)†
Splanchnic vascular resistance (mmHg ml^{-1} min)	7·00 (3·30–11·80)	10·80 (6·36–20·0)†	7·15 (5·22–9·90)

Values are median (range). $^*P = 0·011$; $^†P = 0·024$ (*versus* controls, Mann–Whitney *U* test)

Table 3 *Arteriosystemic and portosystemic shunting in rats with hepatic LV10 and MC28 tumours*

	Controls	LV10	MC28
Arteriosystemic shunting (units)	10 (3–14)	3 (0–12)	13 (1–13)
Portosystemic shunting (units)	10 (0–12)	9 (0–16)	13 (4–15)

Values are median (range)

shunting between rats with hepatic LV10 or MC28 tumours and control animals (*Table 3*).

Mean hepatic replacement

The mean hepatic replacement by weight was 54 per cent for LV10 and 17 per cent for MC28 tumours.

Discussion

Previous studies[1] with hepatic tumour derived from the intraportal inoculation of HSN sarcoma have demonstrated that a reduction in portal venous inflow is the principal cause of the increase in HPI. These studies suggest that neither intrahepatic portal venous obstruction nor arteriosystemic shunting is the cause of these changes in animals with hepatic tumour derived from intraportal inoculation of HSN sarcoma cells, but that circulating splanchnic vasoconstrictors may be responsible for the rise in portal and splanchnic vascular resistance.

The data in the present study support this hypothesis, since the HPI was raised and portal venous inflow decreased in the presence of overt hepatic LV10 tumour. Furthermore, the increases in portal and splanchnic vascular resistance in the presence of LV10 tumour were similar to those previously reported with the HSN tumour. However, the HPI was not significantly increased when overt MC28 tumour was present in the liver, despite a similar degree of hepatic replacement by tumour. In this model portal venous inflow was not decreased and there was no significant rise in splanchnic vascular resistance. If portal venous obstruction were the cause of the changes in HPI then similar changes would be expected in the presence of overt hepatic MC28 tumour. This clearly does not occur.

Since hepatic blood flow is not apparently altered in the presence of MC28 tumour, these observations imply that production of any putative splanchnic vasoconstrictor may be limited to certain types of tumour. Identification of the vasoconstrictor responsible for the changes in liver blood flow in the presence of human colorectal liver metastases may allow easier identification of such secondaries. Furthermore, since these liver blood flow abnormalities are known to occur at the micrometastatic phase of hepatic tumour development[1], before tumours are radiologically detectable, this may allow an alternative means of diagnosing patients at subsequent risk of developing colorectal liver metastases.

Some difficulties with dynamic hepatic scintigraphy in patients have been reported[8], but the authors have recently improved the reproducibility and reliability of the technique in humans by using a radiolabelled colloid with a high administered activity[9] that appears to give clinically useful results. Clearly, further studies are needed both in patients and animal models to identify the precise nature of the splanchnic vasoconstrictor response.

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References

1. Leveson SH, Wiggins PA, Giles GR, Parkin A, Robinson PJ. Deranged liver blood flow patterns in the detection of liver metastases. *Br J Surg* 1985; **72**: 128–30.
2. Hemingway DM, Cooke TG, Grime SJ, Nott DM, Jenkins SA. Changes in hepatic haemodynamics and hepatic perfusion index during the growth and development of hypovascular HSN sarcoma in rats. *Br J Surg* 1991; **78**: 326–30.
3. Healey J. Vascular patterns in human metastatic liver tumors. *Surg Gynecol Obstet* 1965; **120**: 1187–93.
4. Nott DM, Grime SJ, Yates J, Cooke TG, Jenkins SA. Changes in the hepatic perfusion index during the development of experimental liver tumours. *Br J Surg* 1989; **76**: 259–63.
5. Nott DM, Grime SJ, Yates J *et al.* A model of the hepatic perfusion index in the rat. *Nucl Med Commun* 1987; **8**: 990–4.
6. McDevitt DG, Nies AS. Simultaneous measurement of cardiac output and its distribution in the rat. *Cardiovasc Res* 1976; **10**: 494–8.
7. Buckberg GD. Some sources of error in measuring regional blood flow with radioactive microspheres. *J Appl Physiol* 1971; **31**: 398–404.
8. Ballantyne KC, Charnley RM, Perkins AC *et al.* Hepatic perfusion index in the diagnosis of overt metastatic colorectal liver cancer. *Nucl Med Commun* 1990; **11**: 23–8.
9. Hemingway DM, McCurragh G, Bessent RG, McKillop J, Cooke TG. Dynamic hepatic scintigraphy: the effect of high administered activity on reproducibility of HPI. *Nucl Med Commun* 1991; **12**: 811–16.

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Oral calcium inhibits rectal epithelial proliferation in familial adenomatous polyposis

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Calcium reduces colorectal cell turnover and might therefore protect against neoplasia. The inhibitory effects of dietary calcium were tested in a double-blind controlled trial in patients with familial adenomatous polyposis who had undergone previous abdominal colectomy and ileorectal anastomosis. Patients received supplemental calcium carbonate (1500 mg/day) or placebo tablets for 6 months; sigmoidoscopy was performed before and after treatment. Rectal biopsies were maintained in short-term organ culture, and crypt cell production rate (CCPR) was measured stathmokinetically. A total of 25 patients completed the trial; polyp counts were obtained before and after treatment in all and CCPR values in 16. Calcium treatment reduced the mean(s.e.m.) CCPR from 4·72(0·48) to 2·42(0·48) cells per crypt per h ($P < 0{\cdot}05$)*, while values for placebo were unchanged (5·46(1·21)* versus *5·08(1·17) cells per crypt per h). Calcium had no demonstrable effect on the number, size or distribution of rectal polyps. The ability of oral calcium supplementation to suppress rectal epithelial proliferation supports its potential to prevent development of colorectal carcinoma in high-risk individuals.*

Clinical and experimental evidence supports the hypothesis that epithelial hyperplasia is crucial in the development of colorectal neoplasia[1–3]. Patients with familial adenomatous polyposis (FAP) show an expansion in the proliferative zone of colonic crypts[4]; in those with sporadic adenoma or at risk of familial colorectal cancer there is a raised tritiated thymidine labelling index[5]. Kinetic parameters are increased throughout the colon in patients with colorectal adenoma and carcinoma compared with normal subjects[6].

Calcium may reduce colorectal epithelial proliferation and protect against large bowel cancer. The ability of jejunoileal bypass to accelerate crypt cell production rate (CCPR)[7] and enhance experimental colorectal carcinogenesis is negated by doubling the daily oral calcium intake[8]. Evidence in humans suggests that calcium intake > 1500 mg/day is associated with a reduced incidence of colonic cancer[5,9]. In the UK, 500–600 mg/day calcium is considered sufficient for normal health[10] whereas in the USA 800–1000 mg/day is recommended[11]. The western diet may be deficient in calcium, therefore calcium supplements could dampen epithelial proliferation and protect against colorectal cancer.

The effect of oral calcium supplementation was studied in patients at high risk of colorectal cancer by conducting a double-blind controlled trial in patients with FAP. Response was assessed by monitoring adenomatous polyp progression and rectal epithelial proliferation, using the stathmokinetic technique of metaphase arrest in organ culture[12,13].

Patients and methods

Patients

Between January 1990 and June 1991, 28 patients with FAP were recruited into the trial. The median age was 38 (range 16–65) years; there were 19 male and nine female patients. All had previously undergone total abdominal colectomy with ileorectal anastomosis and were under continued surveillance. At the time of entry into the trial, the mean period since colectomy and ileorectal anastomosis was 12 (median 12·5, range 2–30) years. Exclusion criteria included a past history of hypercalcaemia, renal failure or peptic ulceration. Patients were randomized in a double-blind fashion to receive either 1500 mg/day calcium carbonate or an inert placebo (Dalgety Pilsbury, Birmingham, UK) for a 6-month period. During this time they were instructed not to alter their normal diet, and compliance was assessed by a simple questionnaire and by examining returned medication containers.

Entry into the trial did not affect management of rectal polyps, which were simply observed unless they became large. None of the patients recruited was admitted for fulguration during the trial period. Fully informed written consent was obtained from all subjects, and local and regional ethical committee approval was granted before the trial began.

Procedure

A full medical history with special reference to gastrointestinal symptoms and medications was obtained from each patient at the start of the trial. Abdominal and rectal examination and rigid sigmoidoscopy were performed at each visit to the clinic. At sigmoidoscopy the position of the ileorectal anastomosis was visualized and the site, size and number of polyps in rectal quadrants were recorded.

Two adjacent biopsies were taken from macroscopically normal rectal mucosa. The first was transported in culture medium cooled on ice to allow determination of CCPR by an *in vitro* organ culture method. The second was fixed in formalin then stained with haematoxylin and eosin for routine histological examination to exclude the presence of microadenomas. Blood samples were taken to determine serum levels of calcium, phosphate and vitamin D metabolites.

Crypt cell production rate

The rectal CCPR was measured using an *in vitro* organ culture technique as previously described[13,14]. Briefly, rectal biopsies were divided into small explants and set up in organ culture. After 15 h of culture, 0·6 μg/ml vincristine (Oncovin; Eli Lilly, Basingstoke, UK) was added to the culture medium and explants were removed 1, 2 and 3 h later. The tissue was then stained by the Feulgen reaction and individual crypts were isolated by microdissection[15]. The mean number of metaphase arrest figures per crypt was plotted against the time from addition of vincristine; the slope of this line (determined by least squares linear regression analysis) gave a value for the CCPR[13,14] in cells per crypt per hour.

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Serum profiles

To determine vitamin D metabolite levels in the blood, the protein was removed from the serum by precipitation with acetonitrile and the lipid fraction was purified on silica minicolumns (Set-Pak; Waters Chromatography, Milford, Massachusetts, USA). Metabolites were further purified by straight-phase high-pressure liquid chromatography (Zorbax-sil-HPLC; Du Pont, Wilmington, Delaware, USA) and eluted with 96 per cent hexane, 2 per cent methanol and 2 per cent isopropyl alcohol. Levels of $25OHD_3$ were measured using a competitive protein binding assay with diluted rat serum and those of $1,25(OH)_2D_3$ using radioimmunoassay with a specific polyclonal antibody. Calcium, albumin and phosphate levels and liver function were measured by routine laboratory analysis.

Statistical analysis

CCPR values before and after treatment were compared using Student's paired *t* test within treatment groups and the Mann–Whitney *U* test between groups. Polyp counts were assessed using analysis of variance (ANOVA) and the Mann–Whitney *U* test. Serum electrolyte and vitamin D metabolites were compared using the Spearman correlation.

Results

A total of 25 patients completed the trial; three failed to take the tablets regularly and were excluded. Polyp counts before and after treatment were obtained in all 25 patients, and initial rectal CCPR values were measured in 22, one later being excluded because of the finding of microadenomas on histological examination. Paired CCPR values before and after treatment were obtained in 16 patients (nine placebo and seven calcium). The tablets were well tolerated in all subjects, with no reported adverse side-effects.

Crypt cell production rate

There was considerable variation in the 21 pretreatment CCPR values, with a mean(s.e.m.) of 5·96(0·88) (range 1·14–19·80) cells per crypt per h. The placebo had no significant effect on mean(s.e.m.) CCPR, 5·46(1·21) *versus* 5·08(1·17) cells per crypt per h before and after treatment respectively (*Figure 1a*). Calcium, however, reduced mean(s.e.m.) CCPR by 49 per cent, from 4·72(0·48) to 2·42(0·48) cells per crypt per h ($P < 0·05$) (*Figure 1b*).

Polyp counts

The number of rectal polyps varied widely, from absence to almost complete confluence. Oral supplementation with calcium had no significant effect on polyp number, progression or distribution (*Table 1*). The increase in polyp count in patients receiving calcium did not differ significantly from that in the placebo group (47 *versus* 64 per cent).

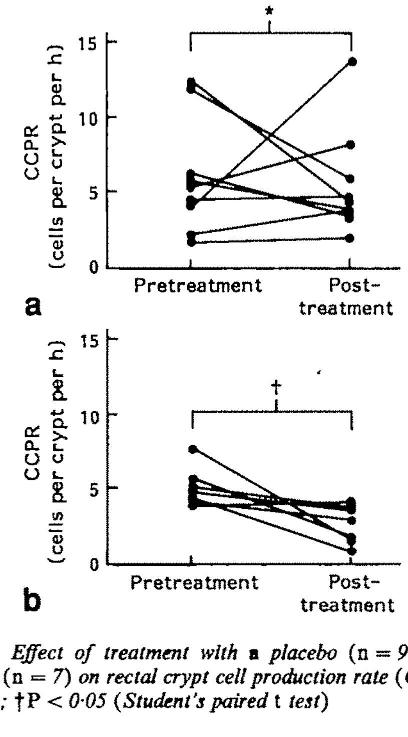

Figure 1 *Effect of treatment with* **a** *placebo* (n = 9) *or* **b** *calcium carbonate* (n = 7) *on rectal crypt cell production rate* (*CCPR*). *P *not significant;* †P < 0·05 (*Student's paired* t *test*)

Table 1 *Effect of calcium carbonate or placebo on number of rectal polyps*

	Before treatment		After treatment	
	Mean(s.e.m.)	Range	Mean(s.e.m.)	Range
Placebo	17·15(5·85)*	2–78	28·09(9·32)	0–100
Calcium carbonate	16·82(7·68)*	0–68	24·68(10·96)	0–100

**P* not significant (before *versus* after treatment, and between treatments)

Table 2 *Serum levels of vitamin D metabolites 6 months after treatment with calcium carbonate or placebo*

	Placebo ($n = 8$)	Calcium carbonate ($n = 5$)
$1,25(OH)_2D_3$ (pg/ml)*	159·21(63·75)	77·40(13·18)‡
$25OHD_3$ (ng/ml)†	69·37(28·35)	28·00(10·31)

Values are mean(s.e.m.). Normal range: *20–65 pg/ml; †3–40 ng/ml. ‡$P < 0·05$ (Spearman correlation test)

Serum calcium and vitamin D

Patients receiving placebo had levels of $1,25(OH)_2D_3$ raised well above the normal range and significantly higher than those in patients given calcium supplements. The value of $25OHD_3$ was above the normal range (3–40 ng/ml), but the difference between the two groups was not statistically significant (*Table 2*).

Serum levels of calcium, phosphate, albumin, bilirubin and liver enzymes were within normal limits in each group.

Discussion

The results of this trial suggest that oral supplementation with calcium carbonate inhibits rectal epithelial proliferation in patients with FAP but has no clear effect on the number of rectal polyps. In a previous uncontrolled trial, calcium supplements in ten subjects at high risk of colorectal cancer reduced the tritiated thymidine labelling index to a value similar to that of individuals in a low-risk group[5]. Further studies have suggested that this effect is seen only in patients whose initial labelling index is higher than normal[16,17]. In five of seven patients with FAP, labelling returned to normal with oral calcium carbonate (1·3–1·5 g/day), and *in vitro* exposure to calcium reduced the labelling indices in three of four patients[17]. Buset *et al.* found that cells cultured from established adenomas did not respond to *in vitro* calcium and neither did those from adenocarcinomas[18]. The present data show that polyp counts are not reduced by calcium, and epithelial cells probably do not respond to the regulatory effects of calcium once adenomatous change has occurred. The presence of microadenomas has been noted on histological examination in patients with FAP[19], and failure to show a reduction in polyp count might reflect continued growth of these early neoplastic lesions.

The present study shows that calcium suppresses the rate of rectal epithelial proliferation in patients with FAP. Similar findings were recently reported in patients with villous adenoma[20]. The results differ from those of a study of patients with previous colorectal cancers but normal labelling indices, in which calcium had no effect on proliferative activity[21]. Six of seven of the present patients responded to calcium, although initial CCPR values (despite a wide scatter) were similar to those previously reported in control subjects[13,22]. The variation in the initial CCPR values may be a true reflection of diverse epithelial proliferation, although multiple biopsies from the same patient would be required to determine the reproducibility of the technique.

Calcium may exert its antitropic effect on colorectal mucosa by binding to free bile acids and fatty acids that would otherwise stimulate cell damage and regeneration[23–25]. Newmark *et al.*[26] postulated that the dietary intake of calcium required to form non-toxic salts of fatty acids and bile acids would need to be doubled from a typical value of 930 mg/day to 1·5–2·0 g/day. Calcium may act in a more complex way, as illustrated by a study in 12 healthy volunteers[27], in which calcium supplements increased faecal excretion of bile acids and phosphate and reduced the dihydroxy bile acid concentration in duodenal bile. These data imply that calcium binds to phosphate in the small intestine and this calcium phosphate complex binds luminal bile acids. Levels of phosphate must also be adequate to allow calcium to exert a protective effect against hyperproliferation. In view of this effect of calcium on duodenal bile, the observed reduction of rectal CCPR could have implications for the control of duodenal polyposis, which has been linked to the distribution of bile acids in the upper gastrointestinal tract[28]. Duodenal cancer is responsible for some deaths in patients with FAP[29–31]. Further work is required to determine whether a reduction in duodenal CCPR will have an effect on polyp formation.

As well as its indirect effect, calcium directly inhibits CCPR in rat and human colon maintained in organ culture[18,32]. Recent work suggests that vitamin D metabolites reduce *in vitro* human rectal CCPR[22], perhaps by a receptor-mediated or a non-genomic effect related to cellular calcium ion flux. Because the patients who received placebo showed vitamin D metabolite levels above the normal range, they may have had intracellular calcium depletion.

Accelerated mucosal proliferation predisposes towards malignancy, so dietary assessment and possible supplementation with calcium could protect against intestinal carcinoma in FAP.

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References

1. Rainey JB, Davies PW, Williamson RCN. Relative effects of ileal resection and bypass on intestinal adaptation and carcinogenesis. *Br J Surg* 1984; **71**: 197–202.
2. Terpstra OT, Dahl EP, Williamson RCN, Ross JS, Malt RA. Colostomy closure promotes cell proliferation and dimethylhydrazine-induced carcinogenesis in rat distal colon. *Gastroenterology* 1981; **81**: 475–80.
3. Rainey JB, Davies PW, Bristol JB, Williamson RCN. Adaptation and carcinogenesis in defunctioned rat colon: divergent effects of faeces and bile acids. *Br J Cancer* 1983; **48**: 477–84.
4. Lipkin M. Biomarkers of increased susceptibility to gastrointestinal cancer: new applications of studies of cancer prevention in human subjects. *Cancer Res* 1988; **48**: 235–45.
5. Lipkin M, Newmark H. Effects of added dietary calcium on colonic epithelial-cell proliferation in subjects at high risk for familial colonic cancer. *N Engl J Med* 1985; **313**: 1381–4.
6. Terpstra OT, Van Blankenkstein M, Dees J, Eilers GAM. Abnormal patterns of cell proliferation in the entire colonic mucosa of patients with colon adenoma or cancer. *Gastroenterology* 1987; **92**: 704–8.
7. Appleton GVN, Bristol JB, Williamson RCN. Increased dietary calcium and small bowel resection have opposite effects on colonic cell turnover. *Br J Surg* 1986; **73**: 1018–21.
8. Appleton GVN, Davies PW, Bristol JB, Williamson RCN. Inhibition of intestinal carcinogenesis by dietary supplementation with calcium. *Br J Surg* 1987; **74**: 523–5.
9. Garland C, Barrett-Connor ER, Shekelle RB, Crique MM, Pual O. Dietary vitamin D and calcium and risk of colorectal cancer. *Lancet* 1985; **i**: 307–9.
10. Hackett AF, Rugg-Gunn AJ, Allinson M, Robinson CJ, Appleton DR, Eastoe JE. The importance of fortification of flour with calcium and the source of calcium in the diet of 375 English adolescents. *Br J Nutr* 1984; **51**: 193–7.
11. Morgan KH, Stampley GL, Zabik ME, Fischer DR. Magnesium and calcium dietary intakes of US population. *J Am Coll Nutr* 1985; **4**: 195–206.
12. Wright NA, Appleton DR. The metaphase arrest technique – a critical review. *Cell Tissue Kinet* 1980; **13**: 643–63.
13. Allan A, Bristol JB, Williamson RCN. Crypt cell production rate in ulcerative proctocolitis: differential increments in remisson and relapse. *Gut* 1985; **26**: 999–1003.
14. Appleton GVN, Wheeler EE, Al-Mufti R, Challacombe DN, Williamson RCN. Rectal hyperplasia after jejunoileal bypass for morbid obesity. *Gut* 1988; **29**: 1544–8.
15. Fergusson A, Sutherland A, MacDonald TT, Allen F. Technique for microdissection and measurement in biopsies of human small intestine. *J Clin Pathol* 1977; **30**: 1068–73.
16. Lipkin M, Friedman E, Winawer SJ, Newmark H. Colonic epithelial cell proliferation in responders and nonresponders to supplementary dietary calcium. *Cancer Res* 1989; **49**: 248–54.
17. Rozen P, Fireman Z, Fine N, Wax Y, Ron E. Oral calcium suppresses increased rectal epithelial proliferation of persons at risk of colorectal cancer. *Gut* 1989; **30**: 650–5.
18. Buset M, Lipkin M, Winawer S, Swaroop S, Friedman E. Inhibition of human colonic epithelial cell proliferation *in-vivo* and *in-vitro* by calcium. *Cancer Res* 1986; **46**: 5426–30.
19. Bradburn DM, Gunn A, Hastings A, Shepherd NA, Chapman PD, Burn J. Histological detection of microadenomas in the diagnosis of familial adenomatous polyposis. *Br J Surg* 1991; **78**: 1394–5.
20. Barsoum GH, Hendricks C, Winslet MC, Donovan IA, Neoptolemos JP, Keighley MRB. Reduction of mucosal crypt cell proliferation in patients with colorectal adenomatous polyps by dietary calcium supplementation. *Br J Surg* 1992; **79**: 581–3.
21. Gregoire RC, Stern H, Yeung KS *et al.* Effect of calcium supplementation on mucosal cell proliferation in high risk patients for colon cancer. *Gut* 1989; **30**: 376–82.
22. Thomas MG, Tebbut S, Williamson RCN. $1,25(OH)_2D_3$ inhibits crypt cell proliferation in human colorectal mucosa. In: Norman AW, Bouillon R, Thomasset M, eds. *Cancer and Vitamin D. Proceedings of the Eighth Workshop on Vitamin D. Vitamin D, Gene Regulation, Structure–Function Analysis and Clinical Application*. Berlin: Walter de Guyer, 1991: 453–4.
23. Wargovich MJ, Eng VWS, Newmark HL. Calcium inhibits the damaging and compensatory proliferative effects of fatty acids on mouse colon epithelium. *Cancer Lett* 1984; **23**: 253–8.
24. Wargovich MJ, Eng VW, Newmark HL, Bruce WR. Calcium ameliorates the toxic effect of deoxycholic acid on colonic epithelium. *Carcinogenesis* 1983; **4**: 1205–7.
25. Rainey JB, Maeda M, Williams C, Williamson RCN. The co-carcinogenic effect of intrarectal deoxycholate in rats is reduced by oral metronidazole. *Br J Cancer* 1984; **49**: 631–6.
26. Newmark HL, Wargovich MJ, Bruce WR. Colon cancer and dietary fat, phosphate and calcium: a hypothesis. *J Natl Cancer Inst* 1984; **72**: 1323–5.
27. Van der Mee R, Welburg JWM, Kuipers F *et al.* Effect of supplemental dietary calcium on the intestinal association of calcium, phosphate, and bile acids. *Gastroenterology* 1990; **99**: 1653–9.
28. Spigelman AD, Williams CB, Talbot IC, Domizio P, Phillips RKS. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet* 1989; **ii**: 783–5.
29. Sinha J, Williamson RCN. Villous adenoma and carcinoma of the duodenum in Gardner's syndrome. *Postgrad Med J* 1988; **64**: 899–902.
30. Jones TR, Nance FC. Periampullary malignancy in Gardner's syndrome. *Ann Surg* 1975; **185**: 565–73.
31. Jagelman DG. Extracolonic manifestations of familial polyposis coli. *Cancer Genet Cytogenet* 1987; **27**: 319–25.
32. Appleton GVN, Owen RW, Wheeler EE, Challacombe DN, Williamson RCN. Effect of dietary calcium on the colonic luminal environment. *Gut* 1991; **32**: 1374–7.

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Carcinoid tumours of the appendix in children 1957–1986: incidence, treatment and outcome

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Forty carcinoid tumours of the appendix were identified in children under 15 years of age between 1957 and 1986 from the records of the West Midlands Regional Children's Tumour Research Group. A significant excess of girls was observed (P = 0·02). *All tumours were discovered incidentally and two patients underwent further surgery. Twenty-two of the 29 confirmed locations (76 per cent) were at the tip of the appendix and 34 of the 40 tumours (85 per cent) had invaded beyond the appendiceal submucosa. The reported incidence rate of 1·14 per million children per year remained constant throughout the study period. No recurrences, metastases or deaths from tumour were detected. Appendicectomy alone is confirmed as usually curative, although right hemicolectomy is occasionally necessary. Caution during routine appendicectomy is recommended to avoid possible tumour damage, as is consistent histological examination of all appendices in the paediatric age group. The importance of long-term follow-up is emphasized.*

In the absence of symptoms of the carcinoid syndrome, tumours of the appendix are never suspected clinically. It has frequently been stated that carcinoid tumours of the appendix are rare in children[1–3], although they are the most frequently found neoplasms of the gastrointestinal tract in childhood and adolescence[4]. They are usually regarded as benign, but it is accepted that they have a potential for malignancy and can metastasize[1,4,5]. Surgery alone is the usual method of treatment, although opinion has varied as to when right hemicolectomy is necessary[5].

The last British study[1] of childhood carcinoid tumours was reported in 1964 and was based on only 15 children from the Scottish Paediatric Tumour Registry. Some subsequent reports[2,5,6] have been confined to patients seen at single centres in the USA and Europe. There are three national European studies[3,7,8], but only three reports[2,3,8] have considered the paediatric age group of patients <15 years of age.

The West Midlands Health Authority region is the largest in England and Wales, with a childhood population[9] in 1981 of 1·12 million. In a larger study of epithelial tumours diagnosed in children aged <15 years in this region[10] there were 40 carcinoid tumours of the appendix in a 30-year period. It was felt that this large series merited separate investigation to assess any changes in incidence or clinical features and outcome since the last British report in 1964, and to allow comparison with data from the other populations.

Patients and methods

A series of children under the age of 15 years with carcinoid tumours of the appendix presenting over a 30-year period was studied, as part of the data collection by the West Midlands Regional Children's Tumour Research Group (Directors: Drs J. R. Mann, M. C. G. Stevens and F. Raafat, and Professor R. K. Griffiths). This group holds data on all cases of childhood cancer that have occurred in the region since 1957, based on the records of the Birmingham and West Midlands Regional Cancer Registry (ascertainment estimated at 95 per cent[11]) supplemented by those of the Children's Cancer Research Group, Oxford, and the oncology and histopathology departments of the Children's Hospital, Birmingham. Review of pathology by specialist paediatric pathologists is carried out on all cases registered to ensure accuracy of the data[12].

Carcinoid tumours were included in a larger study[10] of epithelial neoplasms diagnosed in children in all hospitals throughout the West Midlands between 1957 and 1986. Clinical notes were reviewed for all patients where available ($n = 28$) and follow-up details requested from general practitioners because all patients had been discharged from clinical follow-up. In nine cases the patient's current general practitioner could not be traced and the absence of a death certificate was therefore taken to be evidence that he or she was still alive at the time of the study. All cases of childhood cancer are 'flagged' by the National Health Service Central Register at Southport and a copy of any death certificate for these patients sent to the appropriate regional cancer registry, regardless of the place or cause of death. As no such certificate had been received for present 'lost' patients, they were assumed to be alive.

Pathological material was reviewed by a panel of three specialist paediatric pathologists in 36 cases. In four cases where original material could not be obtained, the recorded clinical and pathological features of the presentation and outcome were studied by the senior pathologist, who confirmed the consistency of the diagnosis.

Incidence rates were calculated using the 1961 census population figure for the decade 1957–1966, 1971 figures for 1967–1976 and 1981 figures for 1977–1986. Assessment of male:female rates was carried out using the binomial test[13].

Results

Carcinoid tumours were found to be the most common of the 136 epithelial neoplasms studied in the larger series[10], with 44 cases diagnosed, 40 of which were located in the appendix. The other four carcinoids were in the bronchus (three) and terminal ileum (one). Incidence rates per million children per year by decade of appendiceal carcinoids were 1·42 for 1957–1966, 1·01 for 1967–1976 and 1·00 for 1977–1986 (*Table 1*). Distribution by age and sex is shown in *Figure 1*.

Appendicectomy rates were not available for 1957–1970, but in the latter half of the study period 24 725 appendicectomies were carried out in children aged <15 years in the West Midlands (13 967 in boys, 10 758 in girls). Twenty-one carcinoids were found, giving an overall detection rate of 0·08 per cent. The number of operations carried out declined from >2600 in 1971 to just over 1600 in 1986. The male:female ratio for patients undergoing appendicectomy was 1·3:1, but

Table 1 *Incidence of appendiceal carcinoid in children by decade*

Decade	Boys	Girls	Total
1957–1966	5 (31)	11 (69)	16
1967–1976	4 (31)	9 (69)	13
1977–1986	3 (27)	8 (73)	11
Total	12 (30)	28 (70)	40

Values in parentheses are percentages

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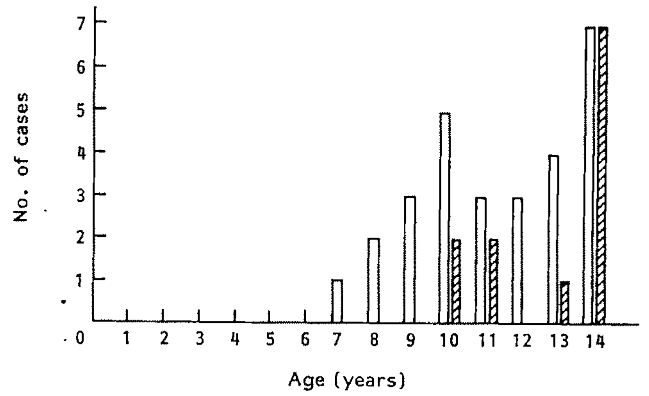

Figure 1 *Carcinoid tumours of the appendix in girls* (☐) *and boys* (■)

the incidence rate of tumours found was 0·03 for boys and 0·11 for girls, showing an excess of the latter ($P = 0{\cdot}02$). There were 28 girls and 12 boys (sex ratio 2·3:1) in the 40 cases of carcinoid tumour studied.

The overall median age was 12·3 (range 7–14) years (*Figure 1*). There was no significant difference between the median age of boys (14 years) and girls (12 years). Presenting symptoms were consistent, with all 40 patients having signs of acute appendicitis. All underwent appendicectomy, although the duration of symptoms varied considerably, from 6 h to 3 years. There was no case of the carcinoid syndrome of flushing, diarrhoea and cardiac irregularities that is usually associated with malignant tumours, especially in the presence of metastases. Vomiting was reported to be present in only 14 children and peritonitis secondary to perforation of the appendix was found in five at the time of surgery. Four patients had experienced similar acute episodes previously, two needing hospital admission. Two other children had had an appendiceal abscess drained 2 and 6 months before surgery.

Thirty-eight children underwent appendicectomy alone. Four tumours were noticed by the surgeon at appendicectomy and in 25 cases the organ was described as normal. No comment was made in the other 11. Of the 36 tumours discovered by the pathologist, only 16 were evident macroscopically. One child underwent re-resection and excision of the caecum and terminal ileum as the original tumour had been cut through at the first operation, a fact that was not noticed until laboratory examination. One tumour discovered on microscopic examination had invaded the whole length of the appendix, which was described as gangrenous, and the patient underwent right hemicolectomy 2 months after initial surgery.

The location of the tumour within the appendix was known in 29 cases; 22 lesions (76 per cent) were found at the tip, with only two at the proximal end. Two tumours were located at the mid-point of the appendix, two were 'eccentric' and one involved the whole length of the organ. The size of the tumour was not always quoted by the original pathologist; of the 15 for which data were available, only three were $\geqslant 1$ cm in diameter, none being >2 cm. One of these tumours was at the mid-point, the other two at the tip.

Only six tumours (15 per cent) were confined to the appendiceal submucosa. Twenty-seven had invaded as far as the subserosa at the time of diagnosis and seven had reached the mesoappendix or appendiceal fat. Threadworms were found in the lumen of the appendix in four children. The pathologists also noted that there were two cases of gangrenous appendix.

There was unanimous agreement between the three pathologists on all 36 specimens reviewed. The other four cases were accepted on the basis of the recorded clinical and pathological features. Three tumours were reported by the reviewing pathologists as showing 'aggressive' features; one of these was in the boy whose tumour involved the whole length of the (gangrenous) appendix and who later underwent right hemicolectomy. Another was found in a girl who underwent a laparotomy at which pelvic peritonitis was discovered. There were no distinguishing features in the third case.

There were no deaths as a result of the tumours and no reports of recurrence or metastatic spread. Follow-up to the present was obtained for 31 of the 40 patients and ranged from 8 to 33 (median 18) years; 20 patients have been followed, and remain disease-free, for >15 years. Nine patients could not be traced, although five of these had already been followed for between 10 and 15 years. One patient had died, a boy diagnosed at the age of 14 years whose tumour was successfully removed and who survived for 12 years free from disease. Death was the result of diabetes mellitus that had never been properly controlled.

Discussion

Willox[1] stated in his British study of 1964 that, in any large series of surgically removed appendices, 0·2–0·5 per cent would contain carcinoids. Moertel *et al.*[4] in 1968 quoted a range of 0·03–0·7 per cent from a survey of the literature and in a subsequent study in the USA[5] in 1987 found an incidence of 0·3 per cent among patients undergoing appendicectomy. The incidence in the present study of 0·08 per cent in children in the West Midlands appears to be lower than rates reported previously, probably because other series included patients of all age groups. Any study that includes adults is likely to show a higher incidence rate because appendiceal carcinoids are usually found incidentally and a large number of gynaecological operations are performed in middle-aged women. The present figure therefore represents the most reliable estimate of incidence in childhood.

Both the observed incidence and age–sex distributions in the present study are relatively constant over the three decades when standardized to the appropriate paediatric populations. It is interesting to observe that the incidence is highest in the first decade, when the appendicectomy rate itself might have been higher, based on the data for the subsequent periods, but the numbers are small and statistical assessment impossible. However, because the vast majority of appendiceal carcinoids do not cause specific symptoms, except in the presence of the carcinoid syndrome, but are discovered incidentally during examination of appendices removed at routine appendicectomy, the incidence rate of the tumour will be influenced by the prevailing appendicectomy and histological examination rates, both of which may have varied over the 30 years of the study period. Appendicectomy rates in the West Midlands have declined gradually, probably influenced by the advent of new diagnostic procedures such as ultrasonography and laparoscopy that have had the effect of reducing the negative appendicectomy rate. The proportion of appendices sent for histological analysis may also have fluctuated with prevailing fashion or local practice, although it is suggested that histological examination should always be carried out in the paediatric age group. As it is not possible to determine the magnitude of such factors reliably, it is not possible to be certain that the actual incidence of appendiceal carcinoids has remained unchanged. However, the present data do represent the best available estimates, as ascertainment with this method of case identification is high.

Population-based incidence rates for carcinoid of the appendix are not generally available for the UK as most registries, including the other specialist paediatric registries in Manchester, Newcastle and Oxford, exclude these tumours because of their usually benign nature. However, the present authors have chosen to include them as they have the potential for malignancy. The present series is believed to give an accurate estimate of the incidence rate in the West Midlands. This region contains one-tenth of the childhood population of the country as a whole, so the rate is likely to be representative nationally.

It has been suggested that the female preponderance of carcinoid tumours of the appendix results from the fact that these tumours are found incidentally at other, usually gynaecological, operations[5]. While this may be true in adults, the girls in the present series were not of an age to undergo such procedures, many not having reached the age of menarche. The significant excess of girls ($P = 0{\cdot}02$) is in accord with results of other paediatric studies[2,3,8]. The male:female ratio of 1·3:1 for appendicectomies carried out during the period shows that the excess cannot be accounted for by larger numbers of girls undergoing this operation.

Carcinoid tumours are rare in the young, although this study identified six children under the age of 10 years, all girls (*Figure 1*). Willox[1] found one child aged 5 years with the tumour and Gorbon and Taspinar[14] in their Turkish study reported a patient 3 years old, the earliest age at which carcinoid has been diagnosed. This was surprising as Stowens[15] was unable to demonstrate argentaffin cells, from which these tumours are believed to arise, in the intestinal tract of children before the age of 4 years. In 1977 Lundqvist and Wilander[16] suggested that appendiceal carcinoids most probably arise from subepithelial argentaffin cells.

All the children in this series presented with symptoms of acute appendicitis, although vomiting was reported to be present in only 14 and nausea without vomiting in two others. Despite the variation in the duration of symptoms there was no suspicion in any child of anything other than appendicitis.

Simple appendicectomy alone was sufficient treatment for all the children with tumours located at the tip of the appendix (22 of 29 known cases), the most common site[3]. Reoperation and excision of the caecum and terminal ileum was necessary for one of the two children with a tumour at the base, as the lesion had been cut through at the first operation. It was felt that further resection was advisable in case of possible metastatic deposits, but no further evidence of tumour was found. The carcinoid was described by the reviewing pathologists as 'aggressive'. This experience implies a need for caution in all appendicectomies, as the presence of a tumour is always a possibility, albeit very rare, and underlines the continuing need for histological examination of all appendices removed from children. Visualization of the appendix at operation is not always sufficient, as demonstrated by the tumour that invaded the whole appendix and yet was found only on histological examination. Right hemicolectomy has been recommended for all tumours >2 cm in diameter[5], as this is felt to be an adverse prognostic factor. None of the tumours in the present paediatric series was recorded as being >2 cm.

The presence of high levels of 5-hydroxytryptamine (5-HT) in the urine in malignant carcinoid syndrome and in association with metastases from carcinoid tumours has been documented[1]. In the present series, confirmation was found in the case notes that seven children were tested for 5-HT after surgery and that the histopathologist recommended this investigation in another three. All who were tested were negative. As metastases are extremely rare, it seems appropriate to measure urinary 5-HT content only in children whose tumours are large or deemed aggressive by the histopathologist.

Despite the fact that threadworms were found in the lumen of four appendices (10 per cent), little or no pathological significance can be attached to this. Budd and Armstrong[17] in a study of appendices removed over a 5-year period found threadworms in 2·5 per cent of cases, while Williams and Dixon[18] found them in 1·5 per cent over a 21-year period. In neither study was the age of the patients specified. Although the incidence in the present series is much greater than these, and twice that of the 5 per cent quoted for inflamed or otherwise normal appendices in children[19], the actual numbers involved are too small to allow valid comparisons.

The degree of invasion of tumours would seem to have no bearing on outcome in children, as there were no metastases or recurrences even though 34 tumours (85 per cent) invaded structures beyond the appendiceal submucosa. Moertel *et al.*[5] suggested in their study of adult and paediatric patients that right hemicolectomy should be carried out where the tumour has invaded the mesoappendix but, in a later evaluation of patients who were under the age of 20 years, recommended that simple appendicectomy was sufficient[6]. The mesoappendix was involved in seven of the present cases, but additional surgery was not performed and the outcome shows that this would have been unnecessary.

Because late recurrence and second malignancies have been reported[4,6] in patients with appendiceal carcinoids, long-term follow-up data are important. Moertel *et al.*[4] reported that only primary tumours >2 cm in diameter had been found to metastasize. None of the present nine 'lost' cases had tumours >2 cm, so it seems unlikely that disease in any would have recurred. As no deaths from tumour or recurrence in this large series of paediatric patients were found, and as 20 children had been followed for between 15 and 33 years, it is concluded that appendicectomy alone is sufficient treatment for the great majority of children, even in the presence of local invasion by the tumour.

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References

1. Willox SW. Carcinoid tumours of the appendix in childhood. *Br J Surg* 1964; **51**: 110–13.
2. Ryden SE, Drake RM, Franciosi RA. Carcinoid tumors of the appendix in children. *Cancer* 1975; **36**: 1538–42.
3. Andersson A, Bergdahl L. Carcinoid tumors of the appendix in children: a report of 25 cases. *Acta Chirurgica Scandinavica* 1977; **143**: 173–5.
4. Moertel CG, Dockerty MB, Judd ES. Carcinoid tumors of the vermiform appendix. *Cancer* 1968; **21**: 270–8.
5. Moertel CG, Weiland LH, Nagorney DM, Dockerty MB. Carcinoid tumor of the appendix: treatment and prognosis. *N Engl J Med* 1987; **317**: 1699–701.
6. Moertel CL, Weiland LH, Telander RL. Carcinoid tumors in the first two decades of life. *J Pediatr Surg* 1990; **25**: 1073–5.
7. Svendsen LB, Bulow S. Carcinoid tumors of the appendix in young patients. *Acta Chirurgica Scandinavica* 1980; **146**: 137–9.
8. Jonsson T, Johannsson JH, Halgrimsson JG. Carcinoid tumors of the appendix in children younger than 16 years. *Acta Chirurgica Scandinavica* 1989; **155**: 113–16.
9. Office of Population Censuses and Surveys. *Census 1981. Key Statistics for Local Authorities. Great Britain.* London: HMSO, 1984: 6.
10. Al-Sheyyab M, Muir KR, Cameron AH *et al.* Malignant epithelial tumours in children: incidence and aetiology. *Med Pediatr Oncol* 1993 (in press).
11. Waterhouse JAH. *Cancer Handbook of Epidemiology and Prognosis.* Edinburgh: Churchill Livingstone, 1974: 4.
12. Muir KR, Parkes SE, Mann JR, Stevens MCG, Cameron AH. Childhood cancer in the West Midlands: incidence and survival, 1980–84 in a multi-ethnic population. *Clin Oncol* 1992; **4**: 177–82.
13. Armitage P, Berry G. *Statistical Methods in Medical Research.* 2nd ed. Oxford: Blackwell Scientific, 1987: 115.
14. Gorbon B, Taspinar AH. Bir appendiks karsinoidinin sebeb oldugu karaciger metastazi. *Turkiye Tip Cemiyeti Mecmuasi* 1963; **29**: 602–7.
15. Stowens D. *Pediatric Pathology.* Baltimore, Maryland: Williams and Wilkins, 1959: 462.
16. Lundqvist M, Wilander E. A study of the histopathogenesis of carcinoid tumours of the small intestine and appendix. *Cancer* 1977; **60**: 201–6.
17. Budd JS, Armstrong C. Role of *Enterobius vermicularis* in the aetiology of appendicitis. *Br J Surg* 1987; **74**: 748–9.
18. Williams DJ, Dixon MF. Sex, *Enterobius vermicularis* and the appendix. *Br J Surg* 1988; **75**: 1225–6.
19. Kissane JM. *Pathology of Infancy and Childhood.* 2nd ed. St Louis, Missouri: Mosby, 1975: 221.

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Treatment of perforated sigmoid diverticulitis: a prospective randomized trial

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A prospective randomized trial was carried out on 62 patients with diffuse peritonitis from perforated diverticulitis of the left colon, comparing acute transverse colostomy, suture and omental covering of a visible perforation with acute resection without primary anastomosis. For purulent peritonitis the postoperative mortality rate was significantly higher after acute resection (six of 25) than after colostomy (none of 21). In those treated by acute resection, the mortality rate was not significantly higher after Hartmann's procedure (five of 15) than after exteriorization of both lumens (one of ten). The postoperative mortality rate in patients with faecal peritonitis did not differ significantly between colostomy (six of ten) and acute resection (two of six). Stomas became permanent in four of 25 patients with diverticulitis surviving acute colostomy and in seven of 22 surviving acute resection. Suture and transverse colostomy is superior to resection for purulent peritonitis because of the lower postoperative mortality rate and in spite of the shorter hospital stay in those surviving acute resection.

Immediate resection of the sigmoid colon for perforated diverticulitis with diffuse, purulent or faecal peritonitis has been recommended[1,2], with or without primary anastomosis. These recommendations are not, however, based on prospective evidence. Retrospective studies suggest that the postoperative mortality rate may be higher after primary resection than after suture of the perforation with a covering transverse colostomy[3,4]. Selection bias can occur and no randomized trial has been published.

This prospective randomized study was initiated in 1978 and was confined to one hospital. The study was designed to investigate differences in morbidity and operative mortality rates between the three-stage procedure (initial suture of the perforation and transverse colostomy) and acute resection without primary anastomosis. An interim report[5] was published in 1986. Because of low recruitment it was decided to stop the trial when 60 patients had been entered.

Patients and methods

The trial was carried out on 62 patients admitted between 1978 and 1992 fulfilling the following four criteria:

1. Diffuse peritonitis with macroscopic signs of diverticulitis of the left colon at laparotomy.
2. Resection of the affected segment possible.
3. Suture of visible colonic perforation possible.
4. No intestinal gangrene.

Criteria for laparotomy were clinical signs of acute peritonitis, although perforated diverticulitis was suspected in no more than 60 per cent of patients before laparotomy. Most of the remainder were suspected of having perforated appendicitis. Faecal peritonitis, shock and advanced age were not criteria for exclusion. Eight patients were treated outside the protocol: six did not fulfil all four criteria but two were erroneously excluded.

Systemic prophylaxis with ampicillin and metronidazole was started when the diagnosis of peritonitis was made before operation or at laparotomy. Pus was cultured and treatment eventually changed according to results. The peritoneal cavity was irrigated with 0·5 per cent chloramine and saline until pus or faeces was no longer apparent. Low-dose heparin was used throughout the study.

Surgery was carried out by 27 consultants or senior registrars supervised by the author. When the abdomen had been opened and the criteria satisfied, randomization was carried out by random number to suture with colostomy or resection. Transverse colostomy was carried out with suture of visible perforation and coverage with an omental flap. After recovery a double-contrast barium enema was administered 4–6 weeks later; elective resection of the inflamed segment followed. The colostomy was closed 2–3 months later when barium enema or colonoscopy had demonstrated an intact anastomosis.

Table 1 *Patient details*

	Suture and colostomy	Acute resection
Sex ratio (M:F)	17:14	10:21 (6:13)*
Age (years)		
Median (range)	71 (37–88)	73 (37–89)
Interquartile range	57–75	58–81
Peritonitis†		
Faecal	10 (6)	6 (2)
Purulent	21 (0)	25 (6)
Visible colonic perforation	24	26

* Values in parentheses are numbers undergoing Hartmann's operation. † Values in parentheses are postoperative deaths

Immediate resection of the inflamed segment was carried out with proximal end colostomy. The distal bowel was placed in the lower part of the main left paramedian incision as a mucus fistula. If the rectosigmoid stump was too short it was closed intraperitoneally by Hartmann's procedure. Elective anastomosis was performed 2–3 months later.

All patients were followed 6 and 12 months after acute surgery and barium enema or colonoscopy performed if colonic symptoms were present.

Statistical methods used were the Mann–Whitney *U* test and Fisher's exact test.

Results

Details of the 62 patients are shown in *Table 1*. A median of 5 (range 3–7) were included each year. Distribution according to age ($P = 0{\cdot}66$) and other severe disease was similar in the groups; most of the complicating diseases were cardiopulmonary.

The proportions of faecal or purulent peritonitis did not differ but postoperative deaths, defined as those within 30 days or during the hospital admission for acute surgery, were more frequent in patients undergoing resection for purulent peritonitis ($P = 0{\cdot}024$). In patients with purulent peritonitis,

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Table 2 *Complications and deaths after acute surgery*

	Suture and colostomy	Acute resection
Cardiopulmonary complications	14	13
Thromboembolism	5	3
Mental confusion	4	4
Wound dehiscence	3	3
Wound infection without dehiscence	4	2
Intraperitoneal abscess	5	4
Dynamic ileus	0	2
Colocutaneous fistula	2	1
Revision of colostomy	0	1
Death within 30 days or during initial hospital stay	6	8

Values are numbers of patients

Table 3 *Final diagnoses*

	Suture and colostomy	Acute resection
Perforated diverticulitis alone	28 (4)	28 (7)
Colonic cancer and perforated diverticulitis	1 (1)	2 (1)
Perforated colonic cancer	1 (1)	0
Colonic infarction	0	1 (0)
Awaiting elective resection	1 (0)	
Total	31 (6)	31 (8)

Values in parentheses are postoperative deaths after acute surgery

Table 4 *Definitive procedures in patients with diverticulitis surviving acute surgery*

	Suture and colostomy	Acute resection
Elective resection	17	
Awaiting elective resection	1	
Closure of colostomy after elective resection	16	
Closure of colostomy without elective resection	4	
Permanent colostomy without elective resection	3	
Anastomosis after acute resection		15
No anastomosis after acute resection		7
Permanent colostomy	4	7

Table 5 *Time in hospital within the first year after acute surgery in patients with diverticulitis, excluding postoperative deaths but including complications and surgery for ventral hernia*

	Suture and colostomy	Acute resection
No. of patients	24	22
Median (range) time in hospital (days)	44 (15–105)	27 (12–54)*

$^*P < 0\cdot0001$ (Mann–Whitney *U* test)

five of 15 died after Hartmann's procedure and one of ten after resection with mucus fistula ($P = 0\cdot34$). The total number of postoperative deaths after Hartmann's operation (seven of 19) was not significantly higher than that after exteriorization of both intestinal lumens (one of 12) ($P = 0\cdot10$). Blood transfusions were given during 13 of 19 Hartmann procedures and in forming four of 12 mucus fistulas; the median duration of the two operations was 135 and 115 min respectively.

Half of the 16 patients with faecal peritonitis died after operation (*Table 1*), no difference being found between the groups ($P = 0\cdot60$). Autopsy was performed in ten of the 14 patients dying after surgery.

Complications and postoperative deaths after initial surgery occurred with similar frequency (*Table 2*). Some patients had more than one complication. The median (range) operating time for suture and colostomy was 105 (45–165) min and for acute resection 130 (75–215) min ($P = 0\cdot001$). Transfusions were given to seven and 17 patients respectively ($P = 0\cdot01$). The subgroup of patients with purulent peritonitis had a shorter time for colostomy ($P = 0\cdot03$) and less frequent use of transfusion (three *versus* 14 patients, $P = 0\cdot01$). Surgical complications such as dynamic ileus, wound dehiscence and intra-abdominal abscess tended to be less frequent after colostomy than resection for purulent peritonitis (three of 21 *versus* seven of 25); the same was true for cardiopulmonary complications (six of 21 *versus* ten of 25).

The diagnosis of perforated diverticulitis was correct in 59 of the 62 patients (*Table 3*), as evaluated by elective surgery or autopsy. Three of the 59 had a cancer within the same colonic segment. One patient initially undergoing suture with colostomy awaits resection.

Elective resection was carried out in 17 of the 25 surviving patients with diverticulitis receiving colostomy (*Table 4*). Four of the remaining eight underwent closure of the colostomy without resection of the inflamed segment. Each had few diverticula and limited radiological signs of diverticulitis. Transverse colostomy was permanent in four patients. In three the risk was considered too high because of postoperative complications and other severe disease.

Elective anastomosis was accomplished in 15 of the 22 patients with diverticulitis surviving acute resection (*Table 4*). Seven were of high risk with various complications and other severe disease; two died 3 and 4 months later from coronary occlusion. Elective surgery was followed by few complications, but wound infection developed in four cases after closure of the stoma. Ventral hernias developed within 1 year in five patients undergoing suture with colostomy and in one receiving acute resection.

The overall time spent in hospital was longer after colostomy (*Table 5*) ($P < 0\cdot0001$). The same was true comparing patients with purulent peritonitis separately (median 42 *versus* 26 days). One patient was excluded from *Table 5*, as he was already in hospital with chronic renal failure.

Of the 46 patients with perforated diverticulitis surviving acute surgery, 42 have been followed for 1 year. One patient had severe recurrent symptoms after closure of a transverse colostomy without preceding resection. The remaining 41 had no or very mild symptoms. Four of the 46 patients have been followed for 6 months without symptoms of recurrence.

Discussion

Violation of the protocol occurred in only two patients and none with abscess was included. Little change in perioperative procedures occurred over the 14 years, making the study of some importance in spite of the small numbers. A total of 466 patients had a clinical diagnosis of acute diverticulitis within the study period but had no signs of diffuse peritonitis or abscess. No more than 15 were subjected to what was demonstrated to be an unnecessary laparotomy because of septicaemia with no peritonitis or abscess. It cannot be proved that perforated diverticulitis has not occurred without clinical signs but this is probably a rare event.

The larger proportion of women undergoing acute resection may produce a bias in favour of this procedure because of the easier dissection in the wide female pelvis. Age distributions were similar and there was no tendency towards more elderly patients undergoing lesser surgery. This was an important bias of earlier retrospective studies[1,6–8] and may explain the higher mortality rate after colostomy. The present higher mortality rate after acute resection for purulent peritonitis may be explained by the longer duration of surgery and the larger blood loss associated with a higher risk of postoperative complications.

The subgroups with faecal peritonitis were too small for analysis, but these patients continue to have a poor prognosis.

In spite of there being more patients with faecal peritonitis undergoing colostomy, the postoperative mortality rate was no higher than in those submitted to primary resection. This may arise from a shorter duration of surgery and less frequent use of transfusion.

Many surgeons took part but diagnostic failures were few; no operation was carried out by registrars.

Closure of the stoma without resection resulted in a high recurrence rate of diverticulitis[9,10]. This may not occur in patients with purulent peritonitis treated with a high-fibre diet after closure[11]. It occurred in one of the present four patients. It is not known how often diverticulitis recurs when the sigmoid colon is permanently defunctioned.

Acute resection for purulent peritonitis has the advantage of shorter hospital stay in those surviving surgery and there is probably a smaller risk of wound infection and ventral hernia. The postoperative mortality rate is, however, comparatively high, making suture and colostomy a better option. No more than one perforated cancer was misdiagnosed in 14 years; this need not support a general recommendation for acute resection.

The 1-year follow-up confirmed the low recurrence rate after limited acute or elective resection[12]. No recurrence was seen in the three patients with permanent colostomy without resection.

The numbers presented are small but comparable to those in other large hospitals[13]. This emphasizes the inadequacy of studies from a single hospital and demonstrates the need for multicentre trials. Because of an increasing number of proponents of primary anastomosis it is difficult to obtain informed consent for a randomized trial with alternatives of colostomy or no colostomy. This study suggests that controls should be those undergoing suture and transverse colostomy, especially if there is purulent peritonitis. The other arm of such a study would include acute resection with primary anastomosis.

Suture and transverse colostomy remains the standard treatment in this department for patients with purulent peritonitis from perforated left-sided diverticulitis demonstrated at laparotomy.

References

1. Krukowski ZH, Matheson NA. Emergency surgery for diverticular disease complicated by generalized and faecal peritonitis: a review. *Br J Surg* 1984; **71**: 921–7.
2. Alanis A, Papanicolaou GK, Tadros RR, Fielding L. Primary resection and anastomosis for treatment of acute diverticulitis. *Dis Colon Rectum* 1989; **32**: 933–9.
3. Berry AR, Turner WH, Mortensen NJMcC, Kettlewell MGW. Emergency surgery for complicated diverticular disease. A five-year experience. *Dis Colon Rectum* 1989; **32**: 849–54.
4. Peoples JB, Vilk DR, Maguire JP, Elliott DW. Reassessment of primary resection of the perforated segment for severe colonic diverticulitis. *Am J Surg* 1990; **159**: 291–4.
5. Kronborg O. Problems involved with a small controlled randomized trial. Two different operative treatments for perforated diverticulitis. *Theoretical Surgery* 1986; **1**: 84–8.
6. Ponka JL. Emergency surgical operations for diverticular disease. *Dis Colon Rectum* 1970; **13**: 235–43.
7. Greif JM, Fried G, McSherry C. Surgical treatment of perforated diverticulitis of the sigmoid colon. *Dis Colon Rectum* 1980; **23**: 483–7.
8. Nagorney DM, Adson MA, Pemberton JH. Sigmoid diverticulitis with perforation and generalized peritonitis. *Dis Colon Rectum* 1985; **28**: 71–5.
9. Brown DB, Toomey WF. Diverticular disease of the colon. A review of 258 cases. *Br J Surg* 1960; **47**: 485–93.
10. Rodkey GV, Welch CE. Surgical management of colonic diverticulitis with free perforation or abscess formation. *Am J Surg* 1969; **117**: 265–9.
11. Drumm J, Clain A. The management of acute colonic diverticulitis with suppurative peritonitis. *Ann R Coll Surg Engl* 1984; **66**: 90–1.
12. Wolff BG, Ready RL, MacCarty RL, Dozois RR, Beart RW. Influence of sigmoid resection on progression of diverticular disease of the colon. *Dis Colon Rectum* 1984; **27**: 645–7.
13. Shephard A, Keighley MRB. Audit of complicated diverticular disease. *Ann R Coll Surg Engl* 1986; **68**: 8–10.

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Anal endosonography and correlation with *in vitro* and *in vivo* anatomy

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The endosonographic anatomy of the anal sphincters was studied by in vivo *and* in vitro *correlation with anatomical dissection. Fourteen fresh anorectal specimens (eight abdominoperineal resection, six post mortem) were scanned in a water-bath with sequential dissection and correlation with the ultrasonographic images. Accurate anatomical identification of the layers during dissection was confirmed histologically. Anal endosonography was performed during operation in 12 patients to validate the* in vitro *findings. The* in vivo *study confirmed the* in vitro *results. Basic endosonographic anatomy has been clarified and inaccuracies in the previous description of the longitudinal muscle and external anal sphincter corrected.*

Endosonography of the anal canal is a new technique[1] that provides detailed images of sphincter defects[2–4] and anorectal sepsis, especially fistula *in ano*[5].

Interpretation depends on understanding the normal sonographic anatomy of the anal sphincters. This has been difficult to establish as initial attempts to correlate results of endosonography with anatomical dissection[1] proved technically unsatisfactory and, despite considerable research, the gross anatomy of the anal sphincters remains controversial. Current views have been summarized by Dalley[6].

The purpose of this study was to define the sonographic anatomy of the anal canal musculature. Resected surgical and post-mortem specimens were used to compare sonographic images with macroscopic dissection. This was combined with histological verification of the different layers. *In vivo* surgical dissection during routine anorectal operations was correlated with simultaneous intraoperative endosonography.

Patients and methods

A B & K Medical (Bracknell, UK) type 1846 ultrasonographic scanner[1] was used with a rectal probe (type 1850) fitted with a 7-MHz transducer (focal length 2–5 cm, 1·1-mm minimal beam width), rotated mechanically to give a 360° cross-sectional image. A hard sonolucent plastic cone of external diameter 1·7 cm covered the transducer and was filled with degassed water for acoustic coupling.

Informed consent was obtained from relatives or patients for *in vitro* and *in vivo* examination.

Studies of surgically resected and post-mortem specimens

Eight abdominoperineal resection specimens (four from women, four from men; age range 46–87 years) and six fresh post-mortem specimens (three from women, three from men; age range 64–89 years) were examined.

In vitro scanning was performed in a water-bath for acoustic coupling, using a modification of the technique described by Beynon *et al.*[7]. Four surgical and two post-mortem specimens were scanned after the anal canal had been opened posteriorly and mounted on to a jig. The jig was made from plastic, measuring 20 × 20 cm, with a 10 × 10-cm section cut out from one side, creating a U shaped former. The specimens were sutured to this via small holes drilled in the plastic. The prepared frame was clamped upright in a water-bath with a second clamp used to hold the ultrasonographic probe close to the specimen.

The echogenic pattern produced by the different layers of the anal canal was determined by scanning after dissection and removal of each layer in sequence, starting with the mucosa and muscularis submucosae ani, the internal anal sphincter, the longitudinal muscle layer and then the external anal sphincter. A biopsy of each layer was taken for histological confirmation.

Three of the surgical specimens had been scanned *in vivo* before abdominoperineal resection. These and one post-mortem specimen were scanned in the water-bath without dividing the anal canal posteriorly. Transverse sections were taken at serial levels along the anal canal to compare histological appearances with corresponding sonographic images.

Intraoperative studies

Anal endosonography was performed in 12 patients (seven men, five women; age range 32–58 years) undergoing surgery for haemorrhoids (four patients), fissures (four), sphincter repair (three) and rectovaginal fistula repair (one). The entire probe was sterilized to allow handling during surgery without risk of contamination.

After skin incision, the lower border of the external sphincter was identified and its lower lateral aspect within the ischioanal (ischiorectal) fossa dissected proximally for a short distance. The probe was then inserted and a stable image of the canal obtained. A pair of flat scissors was placed on the lateral border of the external sphincter and the image recorded, using the acoustic reflection from the scissors for localization. The procedure was repeated for the medial aspect of the external sphincter and outer border of the internal sphincter.

The thickness of individual muscle layers was not measured because there were too many variables in the nature of specimens and examination conditions to ensure consistency of muscle tone.

Results

Resected specimens

The five dissected layers, the subepithelial tissues, internal sphincter, longitudinal muscle, external sphincter and ischioanal fat, were confirmed histologically.

Sonographically bright reflections were seen from interfaces on either side of the plastic cone, creating a well defined hyperechoic double ring (*Figure 1a*). The sonographic patterns produced by the different anatomical layers in both the opened and intact specimens were as follows (*Table 1*; *Figures 1–3*), starting from the mucosa and working outwards:

1. An inner hyperechoic layer that represented the mucosa and subepithelial tissues.
2. Outside the subepithelial tissues there was a well defined uniform hypoechoic ring that corresponded to the internal sphincter.
3. Surrounding the internal sphincter was a hyperechoic layer, thicker than the internal sphincter, and representing the longitudinal muscle and external sphincter.

   The *in vitro* specimens from women studied were from elderly subjects. The longitudinal muscle was macro-

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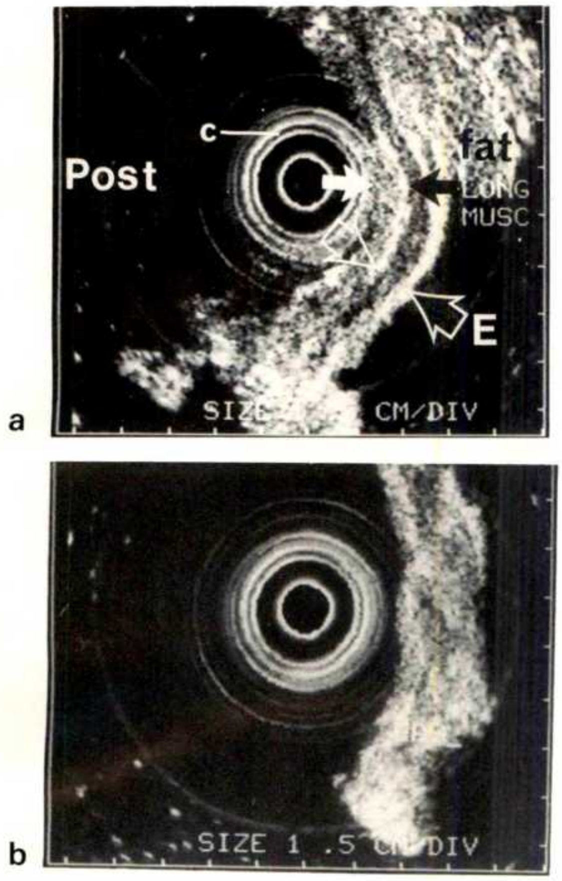

Figure 1 **a** In vitro *scanning in a water-bath of the opened anal canal in a man. Anterior is to the right of the image; Post, posterior. The bright double ring represents the probe cone (c). The internal sphincter has been removed, and the probe is closely applied to the longitudinal muscle (LONG MUSC), seen between closed arrows. In this patient the hyperechoic longitudinal muscle layer is clearly distinguishable from the relatively hypoechoic external sphincter (E), seen between open arrows. Peripheral to the external sphincter is the fat layer.* **b** *Note the change in echogenicity when the specimen in* **a** *was rotated such that the external sphincter fibres lie parallel to the ultrasound beam. The external sphincter can no longer be distinguished from the longitudinal muscle layer*

scopically a rather thin fibrous layer closely adherent to the external sphincter (*Figure 2*) and on ultrasonography similarly hyperechoic. Removal of the longitudinal muscle layer made no discernible difference to the echogenicity of the external sphincter layer.

In specimens from men, the longitudinal muscle layer was thicker although of similar echogenicity. The external sphincter was, however, hypoechoic relative to the longitudinal muscle, so that these two layers could easily be distinguished sonographically (*Figures 1a* and *3*). During dissection of these specimens, many of the external

Table 1 *Endosonography of the anal canal layers*

Layer	Echogenicity
Subepithelial	Hyperechoic
Internal anal sphincter	Hypoechoic
Longitudinal muscle	Hyperechoic
External anal sphincter	Hyperechoic (hypoechoic in most males)
Ischioanal fat	Striated inhomogeneous

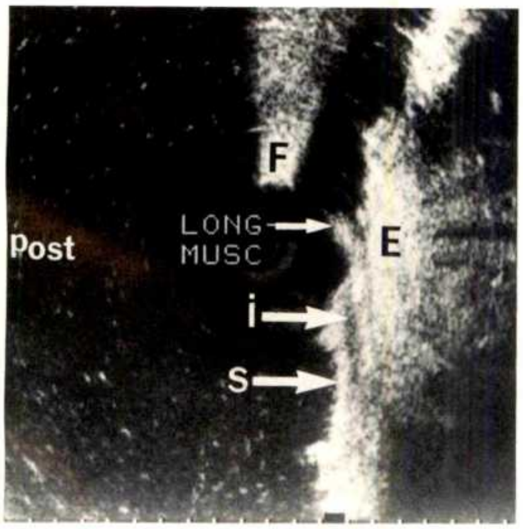

Figure 2 In vitro *scan of the opened anal canal from an elderly woman. Post, posterior; i, internal anal sphincter; E, external anal sphincter; S, muscularis submucosae ani. The longitudinal muscle (LONG MUSC) is held elevated by a forceps (F) from the external sphincter muscle layer. Note that both layers are of similar echogenicity, in contrast to the hypoechoic external sphincter in* Figure 1a

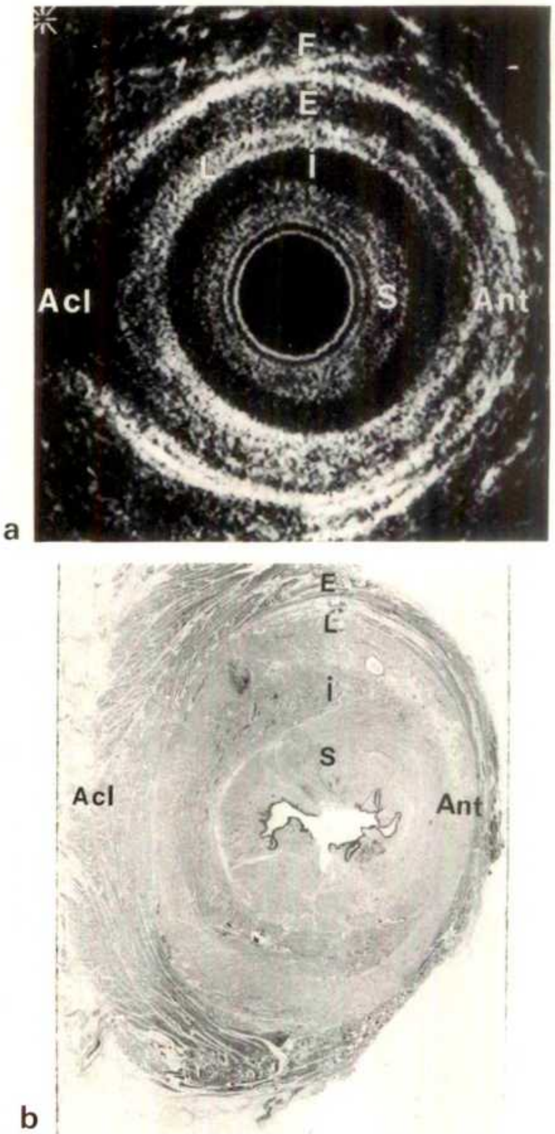

Figure 3 *Cross-section through the mid anal canal in a man. Anterior (Ant) is to the right of the image.* **a** *Endosonographic image.* **b** *Histological cross-section of the anal canal at a comparable level. The fatty layer has disintegrated during preparation of the slide. E, External anal sphincter; L, longitudinal muscle; i, internal anal sphincter; S, muscularis submucosae ani; Acl, anococcygeal ligament; F, fat*

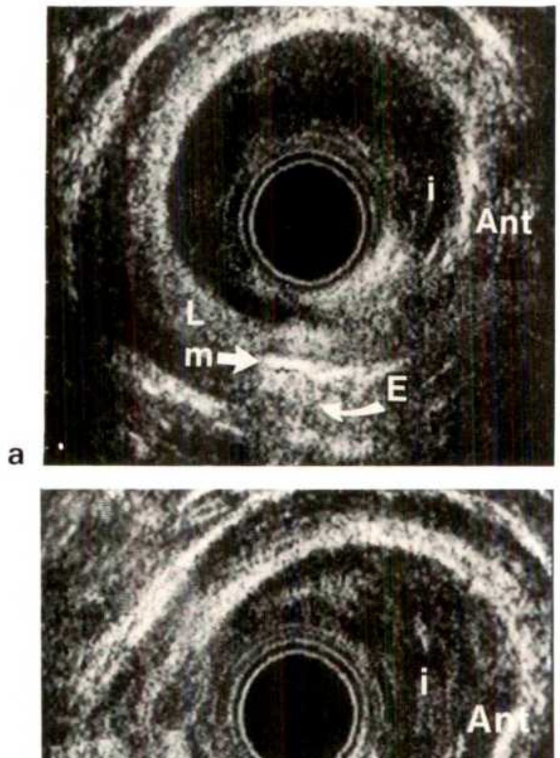

Figure 4 *Image during intraoperative scanning of a man. Anterior (Ant) is to the right of the image.* **a** *The reflection (m) from the scissors placed on the inner aspect of the external sphincter shows that the hyperechoic longitudinal muscle (L) lies medially and the hypoechoic external sphincter (E) laterally.* **b** *The scissors have now been placed on the outer border of the external sphincter, demarcating the external sphincter and fat interface. i, Internal sphincter*

sphincter muscle fibres were observed to run obliquely, a feature not seen in the thinner specimens from women. To establish whether this made any difference to the sonographic appearance of the muscle, a segment of the external sphincter was dissected and aligned such that its fibres were oriented to lie parallel to the ultrasound beam (*Figure 1b*). Compared with *Figure 1a*, it can be seen that the difference in echogenicity between the longitudinal muscle and the external sphincter disappears and both layers appear hyperechoic.

During *in vitro* water-bath dissection the longitudinal muscle was identified sonographically as a separate layer in six of seven specimens from men but in none of those from women, although its presence was confirmed histologically.

4. Outside the external sphincter, irregular linear reflections were seen from the fibrous septa within the adipose tissue of the ischioanal fossa (*Figure 3a*).

Intraoperative studies

The reverberation echo from the flat scissors was clearly visible in all patients. In six of the seven men the external sphincter was hypoechoic (*Figure 4*). Dissection of the intersphincteric space and insertion of the scissors for a short distance confirmed that the outer hypoechoic ring was the external sphincter and that the inner hyperechoic ring represented the longitudinal muscle (*Figure 4a*). In four of five women the external sphincter appeared hyperechoic (*Figure 5*). The internal sphincter was hypoechoic (*Figures 4* and *5*) in all 12 patients.

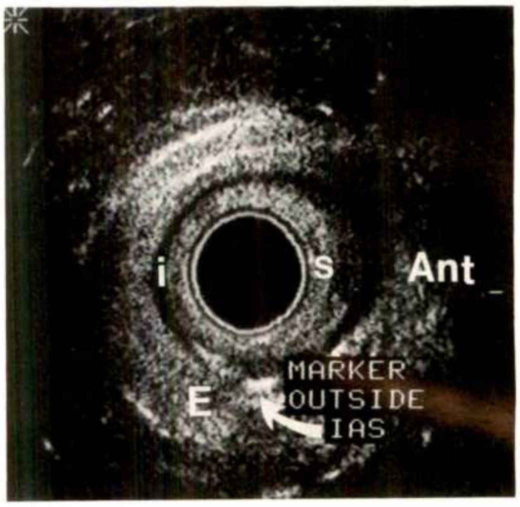

Figure 5 *Intraoperative scanning of a woman. The arrow points to the reflection of the tip of the scissors on the lateral border of the internal sphincter (i). The longitudinal muscle layer in this patient is of similar echogenicity to the surrounding external sphincter (E) and is not distinguishable from it. Ant, anterior; s, submucosa; IAS, internal anal sphincter*

As with the *in vitro* studies, four layers of varying echogenicity were identified. During the *in vivo* operative dissection studies the longitudinal muscle layer was identified sonographically in six of seven men and in one of five women. As with the dissection specimens the longitudinal muscle was identified only when the external sphincter was relatively hypoechoic. Where the external sphincter was hyperechoic, it was impossible to distinguish the layers.

The perineal body was not identified as a distinct sonographic structure in either *in vitro* or *in vivo* studies.

Discussion

There is no muscularis mucosae in the anal canal to separate mucosa from submucosa; hence the term 'subepithelial' to describe these tissues. Anatomical dissection has suggested[8] that there is continuity between the muscularis mucosae of the rectum and superficial fibres of the subepithelial layer in the anal canal, and the term 'muscularis submucosae ani' has been proposed. The mucosa could not be separated from the muscularis submucosae by dissection and was not differentiated as layers endosonographically. Beynon *et al.*[7] were also unable to define the mucosal layer during rectal endosonography. The thickness and echogenic nature of this layer would appear to be below the resolution of the equipment used.

The subepithelial layer (*Figure 2*) and internal sphincter (*Figures 2*, *3a* and *5*) demonstrated a consistent echogenicity. Smooth muscle is generally of low echogenicity and the circular internal sphincter therefore appears hypoechoic. In contrast, the longitudinal muscle was hyperechoic (*Figures 1a*, *3a* and *4*), but this layer could be defined sonographically only when the external sphincter was relatively hypoechoic (*Figures 1a*, *3a* and *4*). This was common in men, but in most of the women studied the external sphincter was hyperechoic, merging inseparably with the longitudinal muscle (*Figures 2* and *5*). These differences in echogenicity could be accounted for by a change in direction of fibres as well as an increase in the fibrous stroma. A similar phenomenon has been demonstrated during ultrasonography of the Achilles tendon, where a change in echogenicity occurs depending on the orientation of fibres in relation to the ultrasound beam[9]. This is likely to explain the differences in the echogenicity of the external sphincter found in this study, particularly between the sexes. During dissection when the anal muscles were well developed, as frequently seen in specimens from men, many of the circular fibres of the external sphincter adopted a more oblique course. This resulted in a change in echogenicity of the external sphincter and hence the hypoechoic appearance relative to the hyperechoic longitudinal muscle (*Figure 1a*). Confirmation of this phenomenon was demonstrated by changing the orientation of the dissected external sphincter layer in relation to the ultrasound beam (*Figure 1b*).

The original description of the endosonographic anatomy of the anal canal[1] confused the intersphincteric space with the longitudinal muscle, and the longitudinal muscle with the outer hypoechoic ring of the external sphincter. It is now recognized that the outer border of the external sphincter is clearly separated from the irregular striated appearance of the septa within the ischioanal fossae (*Figures 3a* and *4b*).

A recent study[10] of anal endosonography combined with simultaneous electromyographic studies confirmed the location of the external anal sphincter, although the longitudinal muscle was not defined. The sphincters have also been imaged using magnetic resonography[11] and the overall appearance of the external sphincter confirmed. Although it was claimed that the longitudinal muscle layer was identified, measurements of the internal sphincter, the subepithelial and longitudinal muscle layers were combined and it is difficult to differentiate the inner layers in the illustrations.

It is evident from the present study that a basic echogenic pattern of the anal canal layers has been defined, with some individual variation and sex difference in the echogenicity of the external sphincter. The inaccuracies in the original description of the sonographic anatomy[1] have been rectified, and abnormalities may now be interpreted with greater precision and confidence.

Acknowledgements

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References

1. Law PJ, Bartram CI. Anal endosonography: technique and normal anatomy. *Gastrointest Radiol* 1989; **14**: 349–53.
2. Law PJ, Kamm MA, Bartram CI. A comparison between electromyography and anal endosonography in mapping external anal sphincter defects. *Dis Colon Rectum* 1990; **33**: 370–3.
3. Burnett SJD, Spence-Jones C, Speakman CTM, Kamm MA, Hudson CN, Bartram CI. Unsuspected sphincter damage following childbirth revealed by anal endosonography. *Br J Radiol* 1991; **64**: 225–7.
4. Law PJ, Kamm MA, Bartram CI. Anal endosonography in the investigation of faecal incontinence. *Br J Surg* 1991; **78**: 312–14.
5. Choen S, Burnett S, Bartram CI, Nicholls RJ. Comparison between anal endosonography and digital examination in the evaluation of anal fistulae. *Br J Surg* 1991; **78**: 445–7.
6. Dalley AF II. The riddle of the sphincters: the morphology of the anorectal mechanism reviewed. *Am Surg* 1987; **53**: 298–306.
7. Beynon J, Foy DMA, Temple JL, Channer J, Mortensen NJMcC. The endosonic appearances of normal colon and rectum. *Dis Colon Rectum* 1986; **29**: 810–13.
8. Fine J, Wickham Lawes CH. On the muscle-fibres of the anal submucosa, with special reference to the pecten band. *Br J Surg* 1940; **27**: 723–7.
9. Fornage BD. Achilles tendon. US examination. *Radiology* 1986; **159**: 759–64.
10. Nielsen MB, Pedersen JF, Hauge C, Rasmussen O, Christiansen J. Endosonograpy of the anal sphincter: findings in healthy volunteers. *AJR Am J Roentgenol* 1991; **157**: 1199–202.
11. Aronson MP, Lee RA, Berquist TH. Anatomy of anal sphincters and related structures in continent women studied with magnetic resonance imaging. *Obstet Gynecol* 1990; **76**: 846–51.

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Colonic bacteria and bacterial translocation in experimental colitis

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The indigenous intestinal flora and an intact mucosa are vital components of body defences against luminal pathogenic bacteria. Disruption of these defences in inflammatory bowel disease may permit bacterial translocation and contribute to disease severity. Support for this hypothesis comes from this study of a hapten-induced rat model of colitis. Induction of colitis was associated with a significantly increased colonic Gram-negative aerobic bacilli count. The results, expressed as log_{10} *[colony-forming units per gram tissue] were: colitic 6·97–8·86* versus *control 4·90–6·69* ($P < 0{\cdot}05$)*. Colitis was also associated with a decreased Gram-positive cocci count at 4·00–8·04* versus *control 6·45–8·30* ($P < 0{\cdot}05$)*. Bacteria translocated to the mesenteric lymph nodes in five of eight colitic rats* ($P = 0{\cdot}01$)*, to the spleen in four* ($P = 0{\cdot}04$) *and to the liver in five* ($P = 0{\cdot}01$) *but to these organs in none of the eight control animals. There was a positive correlation between the severity of colonic inflammation and extent of bacterial translocation in colitic animals* ($r_S = 0{\cdot}86$, $P = 0{\cdot}007$).

The colon is a large reservoir of potentially pathogenic bacteria and endotoxins. Effective defence mechanisms prevent bacteria that colonize the intestine from invading the bloodstream and systemic organs. These mechanisms are mechanical (peristalsis, mucus production, epithelial desquamation, intact epithelial barrier), immunological (secretory immunoglobulins, gut-associated lymphoid tissue) and microbiological (bacterial antagonism, colonization resistance)[1,2].

In inflammatory bowel disease, the intestinal mucosal barrier is disrupted by inflammation and ulceration; there is also evidence that qualitative and quantitative disturbances in the intestinal bacterial flora occur[3–10]. In these circumstances translocation of enteric bacteria and their products through the bowel wall to extraintestinal sites may result. Systemic endotoxaemia has been demonstrated in ulcerative colitis and Crohn's disease and shown to correlate positively with the extent and activity of disease[11–16]. Raised levels of immunoglobulin G to core glycolipid (endotoxin)[16] and immunoglobulin A to bacterial cell peptidoglycans have also been described[17]. Enteric bacteria have been isolated from the mesenteric lymph nodes (MLNs) in patients with Crohn's disease[18] and ulcerative colitis[19]. Gram-negative bacilli have been cultured in the portal blood and from liver biopsies in patients with ulcerative colitis undergoing colectomy[20,21]. In addition, circulating agglutinating antibodies against various enteric bacteria have been identified in Crohn's disease and in active ulcerative colitis[22,23].

The purpose of this study was to investigate whether induction of colitis in the rat causes disruption of the ecology of the indigenous colonic flora and translocation of bacteria from the colonic lumen to systemic organs.

Materials and methods

Animals

Male Wistar rats weighing 300–400 g were used. Animals were housed in individual rack-mounted cages in a room with controlled temperature (22°C) and light–dark cycle (12 h–12 h). Standard rat pelleted formula (Robert Morton, Ballymena, UK) and tap water were provided *ad libitum*.

Induction of colitis

After a 16-h fast, eight rats were sedated by an intramuscular injection of 0·1 ml Hypnorm (fentanyl citrate 0·315 mg/ml, fluanisone 10 mg/ml; Janssen Pharmaceuticals, Oxford, UK) and 0·25 mg diazepam. A 5-Fr polypropylene catheter (Bardic feeding tube 1732; Bard, Sunderland, UK) was lubricated with jelly and inserted 10–12 cm via the anal canal into the colon to lie at, or just proximal to, the splenic flexure. At this point 25 mg 2,4,6-trinitrobenzenesulphonic acid (Sigma Chemicals, Poole, UK) mixed with 0·25 ml 30 per cent ethanol (TNBS–E) was instilled. The catheter was then flushed with 0·5 ml air to expel any remaining inducing agent before being removed. After instillation the rats were supported in a supine Trendelenburg position until recovery from anaesthetic to prevent immediate anal leakage of the instillate.

An additional group of eight normal rats received intracolonic saline and served as healthy controls.

Testing for translocation of bacteria

At 7 days after induction of colitis, the rats were sedated as before and a midline laparotomy performed under sterile conditions.

Portal and systemic blood culture. A sample of 5 ml blood was obtained from both the portal vein and the inferior vena cava for aerobic and anaerobic culture using the radiometric Bactec 460 (Becton–Dickinson, Towson, Maryland, USA). Blood cultures were read on days 1, 2, 4 and 7 at a threshold of 20 for anaerobes and 30 for aerobes. Positive blood cultures were plated out on appropriate media and species identified by standard bacteriological techniques.

Homogenization of organs. The liver, spleen, MLNs from the transverse mesocolon and a 1-cm length of colon from the splenic flexure were removed and placed in preweighed sterile glass bottles containing sterile prereduced brain–heart infusion. The bottles were reweighed and transferred to an anaerobic cabinet (MK3 Anaerobic work station; Don Whitley Scientific, Shipley, UK) where tissue homogenates were prepared in 2 ml brain–heart infusion using sterile mortars and pestels for the spleen, lymph nodes and colon, and a homogenizer (Omni-mixer; Ivan Sorvall, Norwalk, Connecticut, USA) for the liver. Serial dilutions of the colon homogenate ranging from 10^{-3} to 10^{-7} were prepared in brain–heart infusion.

Quantitative and qualitative culture. Aliquots of the homogenates were cultured on blood agar, chocolate agar, McConkey agar, tryptic soy agar and in cooked meat broth. All plates except those for culture of strict anaerobes were removed from the anaerobic cabinet and incubated at 37°C for 2 days. Anaerobes were cultured for 5 days. Aliquots of the broth were plated out the following day on the four standard plates. After the appropriate incubations, individual colonies

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Table 1 *Colon macroscopic score (based on Wallace* et al.[24]*)*

Score	Criteria
0	No damage
1	Hyperaemia
2	Hyperaemia and thickening without ulceration
3	Ulceration at a single site
4	Two or more sites of ulceration or inflammation
5	Ulceration or inflammation extending >1 cm along the length of the colon
6–10	Damage covering >2 cm along the length of the colon, the score being increased by 1 for each additional centimetre of involvement

The excised 1-cm segment not being available for assessment, the remaining portions of the colon were considered as if in continuity

were counted and each organism plated out for purification. Species were identified as before. Micro-organisms were quantified as colony-forming units (c.f.u.) per gram tissue using the formula:

$$\text{c.f.u. per gram tissue} = \frac{N \times D \times 2 \times 10}{W}$$

where N is the number of colonies on the plate, D the dilution inoculated on the plate, W the weight of specimen in grams, 2 for the 2-ml brain–heart infusion and 10 for the 0·1-ml inoculum.

Assessment of colitis

The remainder of the colon was excised, opened longitudinally, and cleared of faecal material with a gentle jet of water.

Colon macroscopic score. The freshly opened colonic segments were pinned out and examined under a dissecting microscope by two independent observers. The extent of mucosal damage was assessed using a modification of the macroscopic scoring system of Wallace *et al.*[24] (*Table 1*).

Colon weight and colon weight:body-weight ratio. After scoring, the distal 8-cm segment of the colon was blotted dry and weighed. The colon weight:body-weight ratio was calculated, as an increase in this ratio has been shown to be an accurate marker of colonic inflammation[25].

Colon histology. The tissue was then fixed using Brunnel's primary fixative (Laboratory Supplies and Instruments, Antrim, UK), processed by conventional methods and then embedded in paraffin. Sections (5 μm) were stained with haematoxylin and eosin and examined using a microscope.

Statistical analysis

Data were assessed using Fisher's exact test, the Mann–Whitney U test, Student's t test and Spearman's rank test. $P < 0{\cdot}05$ was considered significant.

Results

Clinical features

TNBS–E-treated rats showed significant weight loss (*Table 2*), diarrhoea, piloerection, reduced fluid intake, lack of preening, and a reduced level of activity. There was no death in either group.

Colonic inflammation

Significant colonic inflammation was induced in colitic rats compared with the control animals as measured by the colon macroscopic score ($P < 0{\cdot}05$), colon weight ($P < 0{\cdot}001$) and colon weight:body-weight ratio ($P < 0{\cdot}001$) (*Table 2*). Histological examination showed broad-based mucosal ulcers with a surface layer of necrotic ulcer slough. Occasional islands of regenerative mucosa were present. The inflammatory infiltrate associated with the ulcers was mixed, consisting of neutrophils, eosinophils, lymphocytes and plasma cells. Occasional epithelioid granulomas were seen in the ulcer base. The inflammation extended the full thickness of the bowel wall and there was pericolic wrapping of fat. No colonic histological abnormality was identified in the control group.

Colonic flora

The colonic flora in the control and TNBS–E-treated rats were classified according to Gram staining and anaerobiosis (*Table 3*). There was a significant increase in the number of Gram-negative aerobic bacilli and a decrease in the Gram-positive cocci count in colitic rats compared with controls.

Investigation of the relationship between the colonic Gram-negative bacilli count and the colon macroscopic score revealed a positive correlation ($r_S = 0{\cdot}70$, $P = 0{\cdot}05$).

Translocation from the colonic lumen

There was no portal or systemic bacteraemia in control rats. Four colitic rats had positive blood cultures: three portal (*Escherichia coli* in two, a Gram-negative anaerobic bacillus in one) and one systemic (*Pseudomonas aeruginosa*).

Translocation of colonic bacteria to the MLNs, liver and spleen was not seen in the control rats, but did occur to at least one organ in seven of the eight colitic animals. This difference between control and colitic rats was significant for the lymph nodes ($P = 0{\cdot}01$), liver ($P = 0{\cdot}01$) and spleen ($P = 0{\cdot}04$). The distribution and extent of translocation are shown in *Table 4*.

Table 2 *Colonic inflammation and weight gain in control and colitic rats*

	Control ($n = 8$)	Colitic ($n = 8$)	P
Body-weight gain (g)	16·3(2·0)	−14·8(10·9)	0·014*
Colon macroscopic score	0·38(0·21)	7·56(0·51)	<0·05†
Colon weight (g)	0·72(0·10)	2·79(0·31)	<0·001*
Colon weight:body-weight ratio (g/kg)	1·58(0·23)	7·11(0·78)	<0·001*

Values are mean(s.e.m.). *Student's t test; †Mann–Whitney U test

Table 3 *Colonic flora in control and colitic rats*

	Control ($n = 8$)	Colitic ($n = 8$)
Aerobes		
Gram-positive cocci	7·72 (6·45–8·30)	6·08 (4·00–8·04)*
Gram-positive bacilli	8·47 (5·60–9·23)	7·86 (4·00–9·17)
Gram-negative bacilli	6·24 (4·90–6·69)	7·79 (6·97–8·86)*
Anaerobes		
Gram-positive	7·88 (4·00–8·72)	6·95 (4·00–8·52)
Gram-negative	7·52 (4·00–9·20)	8·86 (7·30–9·38)

Values are median (range) $\log_{10}$[colony-forming units per gram colonic tissue]. *$P < 0{\cdot}05$ (Mann–Whitney U test)

Table 4 *Translocation of colonic bacteria in control and colitic rats*

Organ	Translocation incidence*	P‡	Bacterial count ($\log_{10}$[c.f.u. per g])†
MLNs			
Control	0 of 8	0·01	—
Colitic	5 of 8		2·60 (2·00–3·17)
Spleen			
Control	0 of 8	0·04	—
Colitic	4 of 8		2·02 (1·86–2·45)
Liver			
Control	0 of 8	0·01	—
Colitic	5 of 8		2·34 (1·71–2·44)
Blood			
Control	0 of 8	0·04	—
Colitic	4 of 8		—

MLNs, mesenteric lymph nodes; c.f.u. per g, colony-forming units per gram colonic tissue. *Number of positive tests of total animals tested. †Refers to animals whose MLNs contained bacteria; values are median (range). ‡Fisher's exact test

Table 5 *Bacterial species isolated from extracolonic sites in colitic rats*

Rat no.	Mesenteric lymph nodes	Portal blood	Systemic blood	Liver	Spleen
1	—	—	—	*E. coli*	—
2	—	—	—	—	—
3	*E. coli* Anaerobic Gram-negative bacilli	—	—	*E. coli*	*E. coli*
4	Coagulase-negative *Staphylococcus*	*E. coli*	—	*E. coli*	*E. coli*
5	*E. coli* *Vibrella anguillorum*	—	—	—	—
6	*E. coli*	—	*Pseudomonas aeruginosa*	—	—
7	*E. coli* *Acinetobacter lwoffii*	*E. coli*	—	*E. coli*	*E. coli*
8	—	Anaerobic Gram-negative bacilli	—	*E. coli*	*E. coli*

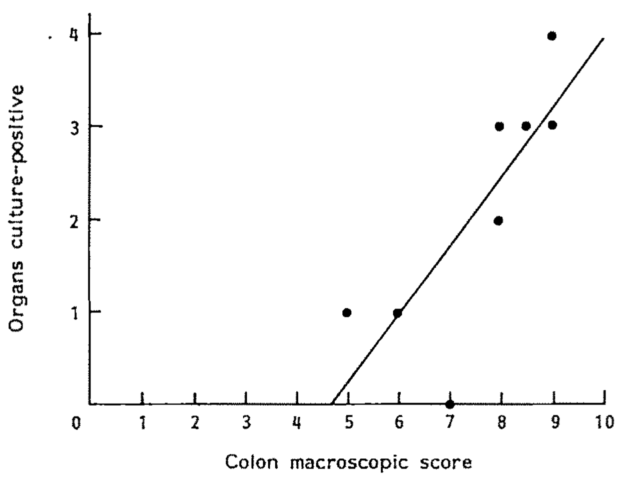

Figure 1 *Extent of bacterial translocation with respect to severity of colonic inflammation in colitis induced by 2,4,6-trinitrobenzenesulphonic acid–ethanol.* $r_S = 0{\cdot}86$, P = 0·007

E. coli was the only organism cultured from the liver and spleen in these rats. In the MLNs, *E. coli* was isolated from four rats and, in addition, there were isolates of *Vibrella anguillorum*, *Acinetobacter* and a Gram-negative anaerobic bacillus. The bacterial species isolated from the extraintestinal sites are summarized in *Table 5*.

The extent of bacterial translocation correlated positively with the colon macroscopic score ($r_S = 0{\cdot}86$, $P = 0{\cdot}007$) (*Figure 1*). No significant correlation was found between the extent of bacterial translocation and $\log_{10}$[Gram-negative bacilli per gram colon] in colitic rats ($r_S = 0{\cdot}36$, $P = 0{\cdot}39$).

Discussion

The bacterial defences of the bowel are associated with two interesting properties of the colonic bacterial flora. The first is the ability to maintain communal stability (bacterial antagonism), which includes such processes as competition for nutrients and adhesion sites, and the production of antimicrobial factors[26]. Second, although serotypes of colonic species such as *E. coli* may change over time, attempts to implant organisms artificially have been largely unsuccessful[27,28]. This ability of the normal intestinal microflora to prevent colonization by exogenous bacteria has been termed colonization resistance[2]. The obligate anaerobes are thought to play an important role in colonization resistance through their close association with the intestinal epithelium constituting a barrier, limiting attachment of potential pathogens to the mucosal epithelium. These bacteria also produce short-chain fatty acids (acetate, propionate, butyrate)[29] that have been shown to provide over 70 per cent of the energy needs of the human colonic mucosa[30]. This anaerobic bacterial barrier and fuel source is lost when broad-spectrum antibiotics are administered[31].

In this study a hapten-induced model of colonic inflammation in the rat (TNBS–E colitis) was investigated. This model has been well characterized and has clinical, biochemical and pathological similarities to colonic Crohn's disease[32]. In addition, it has recently been demonstrated[33] that significant portal and systemic endotoxaemia occurs in this model and persists for at least 3 weeks. The present study provides evidence that induction of colitis by this method is associated with a significant reduction in numbers of aerobic Gram-positive cocci and a significant increase in that of aerobic Gram-negative bacilli within the colon. The colonic aerobic Gram-negative bacilli count also increased with the severity of colonic damage, although this was not statistically significant. These results are in agreement with those reported by Onderdonk *et al.*[34] and van der Waaij and colleagues[35] of a substantial increase in the coliform count within the caecum during the evolution of carrageenan-induced colitis in the guinea-pig. They also correlate well with the disturbances in the colonic flora reported by Ambrose *et al.*[10] and by Keighley and co-workers[7] in colonic Crohn's disease.

Berg and Garlington[36] have described bacterial translocation as the passage of viable bacteria through the epithelial mucosa into the lamina propria, and then to the MLNs and possibly other tissues. Studies have shown that translocation, as measured by the recovery of viable organisms from the regional lymph nodes, is increased by haemorrhagic shock, antibiotic therapy, intestinal obstruction, parenterally administered endotoxin, obstructive jaundice, thermal injury and cytotoxic drugs[37]. Based on these observations, it has been postulated that increased rates of translocation increase the hypermetabolic response of patients with injury and sepsis, cause a septic state in surgical patients in the absence of a defined infectious focus, and predispose or contribute to the development of multisystem organ failure[37]. There appear to be three main mechanisms that promote bacterial translocation: disruption of the ecology of the indigenous gut flora resulting in intestinal bacterial overgrowth[36], impaired host defences[38], and physical damage of the intestinal mucosa[39].

At least two of these factors are features of inflammatory bowel disease, with an obvious physical disruption of the epithelial barrier by inflammation and ulceration and, as outlined above, disturbed bacterial defences with loss of communal stability and reduced colonization resistance. For this reason, the invasion of systemic organs by colonic bacteria in the hapten-induced model of colitis was investigated. In this model both systemic and portal bacteraemia have been demonstrated and it has been shown that bacteria can be cultured from the MLNs, liver and spleen of colitic animals. All the organisms cultured were enteric species. The extent of this translocation of bacteria from the colonic lumen correlated positively with the colon macroscopic score but not with the number of Gram-negative bacilli per gram faeces. This suggests that in this model disruption of the physical barrier is a more important factor than overgrowth of Gram-negative bacilli in promoting bacterial translocation.

Several human studies indicate that bacterial translocation also occurs in inflammatory bowel disease. Aluwihare[40] has reported intramural bacteria in electron microscopic studies of resected ileal tissue in Crohn's disease. Ambrose *et al.*[18] cultured intestinal bacteria from the ileal serosa in 27 per cent and from the mesenteric nodes in 33 per cent of patients undergoing surgery for Crohn's disease. Brooke and Slaney[20] reported positive portal blood cultures in four of nine patients with ulcerative colitis undergoing laparotomy. A subsequent study by Eade and Brooke[21] reported portal bacteraemia in 24 and systemic bacteraemia in one of 100 patients submitted to colectomy for ulcerative colitis. They found that the incidence of positive culture increased directly with the severity of disease. In addition, bacteria were cultured from liver biopsies in 11 per cent of these patients. The most common organisms in all cultures were *E. coli*, *Streptococcus faecalis* and *Proteus* sp.

It has been suggested that bacterial translocation may explain the pathogenesis of abscess and fistula in Crohn's disease and the high incidence of sepsis during elective surgery for inflammatory bowel disease[18], and that it may contribute to the biochemical and histological liver disturbances seen in these conditions[21]. Wellmann *et al.*[14] have used intestinal lavage with normal saline and 5-aminosalicylic acid in patients with Crohn's disease and reported a shorter hospital stay and more rapid decline in disease activity in comparison with a control group. They went on to suggest that these beneficial effects result from a simultaneous reduction in the enteric bacterial microflora and removal of bacterial antigens, thereby reducing translocation of bacteria and endotoxins.

Induction of colitis by intracolonic instillation of TNBS–E is, therefore, associated with a disturbance in the colonic flora, portal and systemic bacteraemia, and translocation of bacteria to systemic organs. Although it is not possible to extrapolate findings from animal colitic models to the human situation, most of these abnormalities have also been reported in inflammatory bowel disease and one may infer that bacterial translocation does occur in this condition. The clinical significance of bacterial translocation and the place of therapeutic strategies such as whole-gut irrigation or mucosal enhancement therapy with short-chain fatty acids are not clear. These issues need to be addressed; this model is suitable for such studies.

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References

1. Walker WA. Role of the mucosal barrier in toxin/microbial attachment to the gastrointestinal tract. In: *Microbial Toxins and Diarrhoeal Disease*. Ciba Foundation Symposium 112. London: Pitman, 1985:34–47.
2. van der Waaij D. Colonization resistance of the digestive tract – mechanisms and clinical consequences. *Nahrung* 1987; **31**: 507–17.
3. Seneca H, Henderson E. Normal intestinal bacteria in ulcerative colitis. *Gastroenterology* 1950; **15**: 34–9.
4. Gorbach SL, Nahas L, Plaut AG, Weinstein L, Patterson JF, Levitan R. Studies of intestinal microflora. V. Fecal microbial ecology in ulcerative colitis and regional enteritis: relationship to severity of disease and chemotherapy. *Gastroenterology* 1968; **54**: 575–87.
5. Cooke EM. Properties of strains of *Escherichia coli* isolated from the faeces of patients with ulcerative colitis, patients with acute diarrhoea and normal persons. *J Pathol Bacteriol* 1968; **95**: 101–13.
6. van der Weil-Korstanje JAA, Winkler KC. The faecal flora in ulcerative colitis. *J Med Microbiol* 1975; **8**: 491–501.
7. Keighley MRB, Arabi Y, Dimock F, Burdon DW, Allan RN, Alexander-Williams J. Influence of inflammatory bowel disease on intestinal microflora. *Gut* 1978; **19**: 1099–104.
8. Dickinson RJ, Varian SA, Axon ATR, Cooke EM. Increased incidence of faecal coliforms with *in vitro* adhesive and invasive properties in patients with ulcerative colitis. *Gut* 1980; **21**: 787–92.
9. Wensinck F, Custers-van Lieshout LMC, Poppelaars-Kustermans PAJ, Schroder AM. The faecal flora of patients with Crohn's disease. *Journal of Hygiene* 1981; **87**: 1–12.
10. Ambrose NS, Youngs D, Burdon DW, Keighley MRB. Changes in intestinal microflora in Crohn's disease. *Br J Surg* 1982; **69**: 681A.
11. Aoki K. A study of endotoxemia in ulcerative colitis and Crohn's disease. I. Clinical study. *Acta Med Okayama* 1978; **32**: 147–58.
12. Colin R, Grancher T, Lemeland J-F *et al.* Recherche d'une endotoxinemie dans les entero-colites inflammatoires cryptogenetiques. *Gastroenterol Clin Biol* 1979; **3**: 15–19.
13. Juhlin L, Krause U, Shelley WB. Endotoxin-induced microclots in ulcerative colitis and Crohn's disease. *Scand J Gastroenterol* 1980; **15**: 311–14.
14. Wellmann W, Fink PC, Benner F, Schmidt FW. Endotoxaemia in active Crohn's disease. Treatment with whole gut irrigation and 5-aminosalicylic acid. *Gut* 1986; **27**: 814–20.
15. Busch J, Hammer M, Brunkhorst R, Wagener P. Endotoxinbestimmung bei entzündlich-rheumatischen Erkrankungen – der Einfluß nichtsteroidaler Antiphlogistika auf die Darmpermeabilität. *Z Rheumatol* 1988; **47**: 156–60.
16. Gardiner KR, Barclay GR, McCaigue MD *et al.* Endotoxin, tumour necrosis factor and anti-core glycolipid antibodies in inflammatory bowel disease. *Br J Surg* 1991; **78**: 1488A.
17. Sartor RB, Cleland DR, Catalona CJ, Schwab JH. Serum antibody to bacterial cell wall peptidoglycan in inflammatory bowel disease patients. *Gastroenterology* 1985; **88**: 1571A.
18. Ambrose NS, Johnson M, Burdon DW, Keighley MRB. Incidence of pathogenic bacteria from mesenteric lymph nodes and ileal serosa during Crohn's disease surgery. *Br J Surg* 1984; **71**: 623–5.
19. Peitzman AB, Udekwu AO, Ochoa J, Smith S. Bacterial translocation in trauma patients. *J Trauma* 1991; **31**: 1083–7.
20. Brooke BN, Slaney G. Portal bacteraemia in ulcerative colitis. *Lancet* 1958; **i**: 1206–7.
21. Eade MN, Brooke BN. Portal bacteraemia in cases of ulcerative colitis submitted to colectomy. *Lancet* 1969; **i**: 1008–9.
22. Heddle RJ, Shearman DJC. Serum antibodies to *Escherichia coli* in patients with ulcerative colitis. *Clin Exp Immunol* 1979; **38**: 22–30.
23. Auer IO, Wensinck ARF, van de Merwe JP. Selected bacterial antibodies in Crohn's disease and ulcerative colitis. *Scand J Gastroenterol* 1983; **18**: 217–23.
24. Wallace JL, MacNaughton WK, Morris GP, Beck PL. Inhibition of leukotriene synthesis markedly accelerates healing in a rat model of inflammatory bowel disease. *Gastroenterology* 1989; **96**: 29–36.
25. Rolandelli RH, Saul SH, Settle RG, Jacobs DO, Trerotola SO, Rombeau JL. Comparison of parenteral nutrition and enteral feeding with pectin in experimental colitis in the rat. *Am J Clin Nutr* 1988; **47**: 715–21.
26. Hentges DJ. Role of the intestinal microflora in host defenses against infection. In: Hentges DJ, ed. *Human Intestinal Microflora in Health and Disease*. New York: Academic Press, 1983: 311–32.
27. Sears HJ, Jones H, Saloum R, Brownlee I, Lamoreaux LF. Persistence of individual strains of *Escherichia coli* in man and dog under varying conditions. *J Bacteriol* 1956; **71**: 370–2.
28. Bohnhoff M, Miller CP, Martin WR. Resistance of mouse's intestinal tract to experimental *Salmonella* infection. I. Factors which interfere with the inhibition of infection by oral inoculation. *J Exp Med* 1964; **120**: 805–16.
29. McNeill NI, Cummings JH, James WPT. Short chain fatty acid absorption by the human large intestine. *Gut* 1978; **19**: 819–22.
30. Roediger WEW. Role of anaerobic bacteria in the metabolic welfare of the colonic mucosa in man. *Gut* 1980; **21**: 793–8.
31. van der Waaij D, de Vries Berghuis JM, Lekkerkerk van der Wees JEC. Colonization resistance of the digestive tract in conventional and antibiotic-treated mice. *Journal of Hygiene* 1971; **69**: 405–11.

32. Morris GP, Beck PL, Herridge MS, Depew WT, Szewczuk MR, Wallace JL. Hapten-induced model of chronic inflammation and ulceration in the rat colon. *Gastroenterology* 1989; **96**: 795–803.
33. Gardiner KR, Anderson NH, McCaigue MD, Halliday MI, Rowlands BJ. Systemic endotoxaemia in experimental colitis and following treatment with oral lactulose. *Br J Surg* 1990; **77**: 1421A.
34. Onderdonk AB, Hermos JA, Dzink JL, Bartlett JG. Protective effect of metronidazole in experimental ulcerative colitis. *Gastroenterology* 1978; **74**: 521–6.
35. van der Waaij D, Cohen BJ, Anver MR. Mitigation of experimental inflammatory bowel disease in guinea pigs by selective elimination of the aerobic Gram-negative intestinal microflora. *Gastroenterology* 1974; **67**: 460–72.
36. Berg RD, Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. *Infect Immun* 1979; **23**: 403–11.
37. Deitch EA. Bacterial translocation of the gut flora. *J Trauma* 1990; **30**: S184–9.
38. Deitch EA, Maejima K, Berg RD. Effect of oral antibiotics and bacterial overgrowth on the translocation of the GI tract microflora in burned rats. *J Trauma* 1985; **25**: 385–92.
39. Deitch EA. The immunocompromized host. *Surg Clin North Am* 1988; **68**: 181–90.
40. Aluwihare APR. Electron microscopy in Crohn's disease. *Gut* 1971; **12**: 509–18.

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Intraoperative irrigation for acute distal colonic obstruction caused by carcinoma

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Irrigation during surgery for distal colonic obstruction is easy when proximal segments of the colon are distended with gas and liquid faeces and can thus be cleared with minimal manipulation[1–5]. Sometimes, however, a segment of colon 15–20 cm in length, immediately proximal to an obstructing carcinoma, may be filled with large and hard faecal masses. In this situation, intraoperative irrigation using glass tubes is very difficult[1]. If soft pliable anaesthetic scavenger tubes are used, excessive kneading may lead to faecal spillage as a result of tube dislodgement, and enthusiastic manipulation of a dilated colon may result in colonic tears and perforation.

A prolonged operating time may be necessary, involving large volumes of irrigation fluid and extensive bowel manipulation, with an increased potential for intraoperative and postoperative morbidity. Direct discharge of irrigation effluent into an open receptacle[2] is offensive, and the collection of large volumes of irrigation fluid and faeces may contaminate the operative field and theatre environment. An isolation bag[2,5] to collect lavage effluent in a closed system cannot be secured easily to the colon without the use of tubes to support the colonic wall.

A solution to this problem is presented.

Surgical technique

The left colon is mobilized according to surgical oncological principles. Early mobilization of the splenic flexure before colonic irrigation is, however, unnecessary in most patients with a rectosigmoid or distal sigmoid tumour. To ensure a tension-free anastomosis, splenic flexure mobilization is better performed following colonic irrigation. Hard faecal masses proximal to the tumour are 'milked' backwards from the lesion for a short distance and a linear stapler applied to transect this segment of colon. The collapsed distal segment with the tumour can then be easily resected. Mechanical staplers are less obtrusive than intestinal clamps and less likely to slip during subsequent tumour resection. The colon is palpated and a pair of non-crushing intestinal clamps placed just proximal to the junction between the hard and liquid faecal matter. The proximal segment of colon containing the hard faecal matter can then be delivered outside the abdomen into a kidney dish placed at the side of the patient, after further colonic mobilization if necessary. The stapled distal end of the colon within the kidney dish is opened with scissors and the hard faecal scybala 'milked' into the dish, taking care to avoid spillage. After evacuation of these hard faecal masses, intraoperative irrigation can be performed according to the usual practice with either glass or soft tubings as outflow channels[1,3].

Initial evacuation of hard faecal masses before intraoperative irrigation reduces colonic manipulation and irrigation fluid requirements and may decrease intraoperative complications and postoperative morbidity.

References

1. Tan SG, Nambiar R, Rauff A, Ngoi SS, Goh HS. Primary resection and anastomosis in obstructed descending colon due to cancer. *Arch Surg* 1991; **126**: 748–51.
2. Donaldson DR, Hughes LE. Notes on 'on table' lavage. *Br J Surg* 1987; **74**: 465.
3. Dudley HAF, Radcliffe AG, McGeehan D. Intraoperative irrigation of the colon to permit primary anastomosis. *Br J Surg* 1980; **67**: 80–1.
4. Muir EG. Safety in colonic resection. *Proc R Soc Med* 1968; **61**: 401–8.
5. Gramegna A, Saccomani G. On-table colonic irrigation in the treatment of left-sided large-bowel emergencies. *Dis Colon Rectum* 1989; **32**: 585–7.

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The Vascular Surgical Society of Great Britain and Ireland

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The following abstracts are from the papers presented at the 26th Annual Meeting of the Vascular Surgical Society of Great Britain and Ireland, held in London, UK, on 4–6 November 1992.

Candidate genes for abdominal aortic aneurysm

J.T. Powell, R.M. Greenhalgh, S.E. Humphries and A. Henney, *Charing Cross Hospital and Rayne Institute, London, UK*

The strong familial tendency to abdominal aortic aneurysm (AAA) may have both a genetic and an environmental basis. The association of three candidate genes with AAA was investigated: type III collagen (mutations associated with Ehlers–Danlos type IV syndrome), fibrillin (mutations associated with Marfan's syndrome) and elastin.

Genomic DNA was prepared from the peripheral leucocytes of 145 patients with AAA, 84 patients with aortoiliac stenosis and 88 age- and sex-matched controls without AAA or aortoiliac disease. DNA was analysed for the presence of two polymorphic restriction sites in the type III collagen gene and variable tandem repeats in the elastin and fibrillin genes. DNA from patients with AAA was also screened for the Gly-619 type III collagen mutation found in an American family with aortic aneurysm.

The frequency of the two polymorphic variants of the type III collagen gene was similar in patients with AAA, aortoiliac stenosis and the normal population. The Gly-619 type III collagen mutation was not observed in any patient with AAA. The variable repeat studied in the fibrillin gene on chromosome 15 shows four alleles. The frequency of these four alleles was similar in patients with AAA, aortoiliac stenosis and older controls. The CA repeat studied in the elastin gene has eight alleles; their distribution was similar in patients with AAA and aortoiliac stenosis.

It is unlikely that a single common founder mutation in type III collagen, fibrillin or elastin contributes to the development of most AAAs. Future studies must focus on the search for specific mutations using affected siblings with AAA.

Computer decision support for vascular surgery

C.J. Ranaboldo, J. Davies and A.D.B. Chant, *Southampton University Hospital, Southampton, UK*

Recent progress in computer and software technology has allowed new approaches to the implementation of computer decision support systems for clinical practice. These developments suggest that it may be possible to provide computer-generated advice about the management of individual patients with vascular disease. This report examines the feasibility of the approach, the quality of the information generated and its relevance to clinical practice.

The computer system that has been developed, using principally model-based reasoning, takes information about individual patients held within an extensive computer-based vascular registry to generate a model of the patient's case. The system uses facts from a vascular knowledge-base that contains information about outcome for both the authors' patients and those from published series. Advice is given regarding necessary investigations, fitness for proposed procedures, risks of possible treatments and, for patients with abdominal aortic aneurysm, prediction of the likely outcome.

For 108 patients held within the authors' registry, the system generated an accurate model of the case in 106 (98 per cent). It highlighted omissions in the investigation strategy in 16 per cent of cases and excessive investigation in 22 per cent. Of 160 clinical problems, 134 were correctly identified, with no important clinical points being missed. The system's assessment of fitness for surgery, based on a modified scoring system, related closely to actual clinical events ($\chi^2 = 5{\cdot}78$, $P < 0{\cdot}05$).

The model extracted appropriate information from both the local vascular registry and the vascular knowledge-base in 94 per cent of cases. In the case of patients with aortic aneurysm ($n = 54$) advice about management differed from actual treatment in six cases, with a recommendation to monitor the patient rather than to operate. One of these patients died and two had cardiac events as complications of surgery.

The development of model-based decision support systems for use in vascular surgical practice is now feasible. In addition to capturing clinical information, such systems are capable of auditing it and using the results of that audit to feed back directly into the unit's decision-making process.

Glasgow aneurysm score

A.K. Samy and G. McBain, *Southern General Hospital, Glasgow, UK*

It is accepted that there is a worldwide increase in the incidence of abdominal aortic aneurysm (AAA). It is also clear that the management of most of these aneurysms, for the conceivable future, will fall on the shoulders of general surgeons. It would be of value, therefore, to establish a prognostic scoring system to assist in the management of such patients. This was the main aim of the study presented.

Randomly selected case notes of 500 consecutive patients with AAA, representing 41·6 per cent (500 of 1202) of the total disease population treated in the general surgical units of Glasgow (as opposed to purely vascular units) between 1980 and 1990, were examined for all possible risk factors. These were then related to the operative and postoperative hospital mortality rates. Initial univariate analysis showed the outcome to be significantly influenced by the following factors: age ($P = 0{\cdot}01$), rupture ($P < 0{\cdot}001$), shock ($P < 0{\cdot}001$), myocardial disease ($P = 0{\cdot}08$), cerebrovascular disease ($P = 0{\cdot}03$), renal disease ($P = 0{\cdot}03$) and size of aneurysm ($P = 0{\cdot}06$). By using multivariate analysis, the following independent risk factors were identified: age ($P = 0{\cdot}02$), shock ($P < 0{\cdot}001$), myocardial disease ($P = 0{\cdot}02$), cerebrovascular disease ($P = 0{\cdot}02$) and renal disease ($P = 0{\cdot}003$). By rounding the regression coefficients a simple risk score was created:

$$\begin{aligned}\text{risk score} = {} & (\text{age in years}) + (17 \text{ for shock})\\ & + (7 \text{ for myocardial disease})\\ & + (10 \text{ for cerebrovascular disease})\\ & + (14 \text{ for renal disease})\end{aligned}$$

Retrospective evaluation of the scoring system showed that the mortality rate rises in proportion to the score.

Gastric intramucosal pH in prediction of outcome after surgery for ruptured abdominal aortic aneurysm

N. Maynard, P. Taylor, D. Bihari and R. Mason, *Guy's Hospital, London, UK*

The mortality rate associated with repair of ruptured abdominal aortic aneurysm (AAA) remains high despite advances in anaesthetic, surgical and intensive care techniques. Many deaths result from multiple organ failure, which is likely to be related to splanchnic ischaemia.

Conventional assessment of tissue oxygenation is by measurement of haemodynamic parameters (cardiac index, mean arterial pressure, heart rate, central venous pressure, pulmonary artery occlusion pressure), oxygen delivery and consumption, and metabolic markers (arterial pH, lactate level, base excess), but these take no account of regional, especially splanchnic, variations in oxygen delivery, which may be significant. The intramucosal pH (pH_i) of the stomach can now be measured indirectly with a nasogastrically placed tonometer, providing an indication of the adequacy of splanchnic oxygenation.

Twenty-two patients admitted to the intensive care unit following surgery for ruptured AAA had all the above parameters measured serially, together with assessment of the gastric pH_i. The mean 24-h APACHE II score was 19·7 and the mortality rate 46 per cent. There were no significant differences in any parameter between patients who died and those who survived apart from gastric pH_i measured 24 h after admission. Survivors had a mean pH_i of 7·4 compared with 7·2 in those who died ($P < 0{\cdot}001$). In survivors who had a low pH_i on admission there was a significant improvement over the first 24 h (from 7·2 to 7·4, $P < 0{\cdot}05$), which was not seen in patients who subsequently died. Measurement of pH_i had a sensitivity of 89 per cent and specificity of 85 per cent, with a likelihood ratio (sensitivity:false positivity) of

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5·9 for predicting death – all higher than for any other variable measured.

Gastric $\mathrm{pH_i}$ is the most sensitive measurement for predicting outcome in these patients, suggesting that splanchnic ischaemia may have an important role in determining survival. Measurement of gastric $\mathrm{pH_i}$ may help in the difficult decisions involved in the postoperative management of patients with ruptured AAA.

Abdominal aortic aneurysm screening: acceptance rates, false negatives and age-related incidence in 2116 patients

R.A.P. Scott and H.A. Ashton, *St Richard's Hospital, Chichester, UK*

Ultrasonographic screening of the male population at the age of 65 years has been proposed as a cost-effective method for the detection of abdominal aortic aneurysm (AAA). Review of the mortality data for the authors' district over 3 years demonstrated that 97·2 per cent of deaths from ruptured AAA occur at or after the age of 65 years. A single scan at the age of 65 years has shown a high acceptance rate in this younger group of patients, who have the most to benefit from surgery. Screening once only at this single age window is cheaper than screening the whole at-risk population.

Observations with ultrasonography on 5392 men and women aged 65–80 years in a general practice population have shown that the incidence of AAA increases with age in men, from 5·9 per cent at 65 years to 9·0 per cent at 71–75 years. A similar increase is apparent in women, although the incidence is lower. In a separate study, 2166 patients were offered screening as they reached the age of 65 years, and 1374 were scanned (acceptance rate 63 per cent). AAAs were initially detected in 5·1 per cent of men and 0·4 per cent of women aged 65 years. Patients with a normal aorta at the initial scan were rescreened after 2 years and 0·9 per cent were found to have an AAA on the repeat scan.

These findings suggest that, while a single screening of men at the age of 65 years will identify the vast majority of those at risk from rupture, it is unlikely to detect one-third of those who subsequently develop AAA up to the age of 75 years.

Eventual outcome for 112 men with screen-detected abdominal aortic aneurysm less than 4 cm in diameter

J. Collin, B. Heather, J. Walton and E. Shaw, *The John Radcliffe Hospital, Oxford, UK*

Two-thirds of abdominal aortic aneurysms (AAAs) detected by screening programmes are $<4·0$ cm in diameter. The long-term outcome for these patients is unknown but will dictate future management decisions for the increasing number of small aneurysms currently being diagnosed by screening.

A total of 112 men with AAA $<4·0$ cm in diameter (median 3·0 (range 2·5–3·9) cm) have been followed for a minimum of 2·5 years from screening. All were invited 6 monthly for ultrasonographic follow-up, and the eventual outcome to March 1992 was recorded.

Six men refused follow-up, but all are alive. Eighty patients are still attending for 6-monthly ultrasonography, of whom 14 have an AAA at least 4 cm in diameter (median 4·4 cm, maximum 5·0 cm). Ten patients have survived elective surgery for AAA of median diameter 4·7 (range 4·2–5·7) cm, and one patient with severe cardiac and respiratory disease died following surgery for an AAA 6·7 cm in diameter. Fifteen men have died without surgery, two from ruptured aneurysm; one was confirmed at autopsy but only one other autopsy was performed. The mean(s.e.m.) annual increase in AAA diameter for the 80 men still under review was 0·11(0·01) cm and for the 11 undergoing operation 0·64(0·01) cm ($P < 0·0001$).

It is concluded that within 3 years of diagnosis one-quarter of all screen-detected AAAs $<4·0$ cm in initial diameter will have become clinically significant. Careful clinical assessment of all patients with clinically significant aneurysms is essential, and elective surgery is likely to be appropriate in 40 per cent of cases.

Prospective audit of surgery for aortic aneurysm

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Over a 4-year period a prospective audit was carried out on 817 patients (657 men of mean(s.d.) age 69(8) years, 160 women of mean(s.d.) age 72(7) years). A total of 325 operations were performed in teaching hospitals and 492 in district hospitals. Emergency operations accounted for between 34 per cent (teaching hospitals) and 44 per cent (district). Overall, 60 per cent of grafts were straight. There were no overall differences in mortality rates between patients with straight and bifurcated grafts.

The overall mortality rates for emergency cases were 59 per cent (teaching hospitals) and 42 per cent (district). Mortality rates for elective surgery were reversed, 5 and 11 per cent respectively. However, for the last complete years these rates have improved to 46 per cent for emergency and 4 per cent for elective cases (teaching hospitals). Seventy-three patients (9 per cent) were admitted with an alternative diagnosis, ranging from collapse of unknown cause (25) and renal colic (14) to torsion of the testis (one) and even colonic obstruction (one).

After operation 77 patients (9 per cent) developed deterioration of renal function, some requiring dialysis. Perioperative myocardial infarction occurred in 6 per cent, and 4 per cent required relaparotomy for either haemorrhage, ischaemic bowel or obstructed bowel. Eleven patients (1 per cent) suffered a cerebrovascular accident. Emergency cases referred via casualty were less likely to survive (39 per cent) than those admitted via the urology department (67 per cent) or from their general practitioner (53 per cent). Age had a profound effect on mortality. The emergency mortality rate varied from 46 per cent in those aged <80 years to 62 per cent in those aged $\geqslant 80$ years ($P = 0·09$). Elective surgery also carried an increased mortality rate, from 7 per cent in patients <80 years to 27 per cent in those $\geqslant 80$ years ($P = 0·0006$).

Earlier accurate diagnosis may help further to reduce the mortality rate associated with emergency aortic aneurysm surgery. Prospective audit suggests that patients aged >60 years, presenting particularly with collapse, renal colic or unexplained abdominal pain, should have urgent aortic ultrasonography to avoid missing a ruptured aneurysm. Finally, these data refute the argument, suggested in the Confidential Enquiry into Perioperative Deaths report, that aneurysm surgery should not be performed in patients over 80 years old, as 38 per cent survive and leave hospital.

Moderate hypothermia protects against spinal cord ischaemia

A. Qureshi, D.M. McCoy, M.A. Black, P.A. Grace, R. Dwyer and D. Bouchier-Hayes, *Beaumont Hospital, Dublin, Ireland*

The incidence of paraplegia resulting from spinal cord ischaemia during thoracic aortic cross-clamping is 40 per cent. Lowering brain temperature by only a few degrees during ischaemia is known to confer a marked protective effect. The influence of moderate hypothermia on neurological outcome after spinal cord ischaemia was investigated.

Twelve dogs breathing nitrous oxide, 66 per cent in oxygen, received 1·3 per cent end-tidal isoflurane. After thoracotomy, the descending thoracic aorta was cross-clamped for 30 min. Mean arterial pressure (MAP) was monitored proximally and distally to the cross-clamp, and pulmonary artery pressures and cardiac output were measured. Cerebrospinal fluid pressure (CSFP) was measured via a needle inserted in the cisterna magna. Sodium nitroprusside (2–10 μg kg^{-1} min^{-1}) maintained the proximal MAP in the range 100–120 mmHg. In the hypothermia group ($n = 7$) (randomly assigned), body temperature (measured by pulmonary artery thermistor probe) was reduced to 35°C by packing the thorax with ice before cross-clamping, and this level was maintained with cooled intravenous normal saline infusion during the ischaemic insult. In the control group ($n = 5$) temperature was maintained at preclamp levels (38°C) using an overhead lamp and heating blanket. Neurological status was assessed 24 h later by scoring motor function in the hind legs (Tarlof scale: 0, fully paralysed; 4, no neurological deficit).

	MAP (mmHg)*			Median Tarlof
Group	Proximal	Distal	CSFP*	score
Control	110(11)	16(8)	19(8)	0
Hypothermia	107(18)	17(5)	20(7)	2†

*Values are mean(s.d.). †$P < 0·05$ (Mann–Whitney U test)

Proximal and distal MAP, CSFP and spinal cord perfusion pressure did not differ between groups. However, neurological outcomes were significantly different: Tarlof score was zero in the control group *versus* 2 in the hypothermic animals. It is concluded that moderate hypothermia protects against spinal cord ischaemia resulting from decreased perfusion pressure during thoracic aortic cross-clamping.

Pulmonary trapping of activated neutrophils following aneurysm repair

I.S. Paterson, J.M. Klausner, J.A. Mannick and H.B. Hechtman, *Queen Elizabeth Hospital, Birmingham, UK and Brigham and Women's Hospital, Boston, Massachusetts, USA*

Reperfusion of ischaemic tissue during aortic aneurysm repair generates thromboxane, activates neutrophils and leads to multiple organ dysfunction. The lung, however, is disproportionately damaged. This study examined the hypothesis that the more activated neutrophils leaving the ischaemic lower limbs are trapped by the lung.

Eighteen patients undergoing elective infrarenal abdominal aortic aneurysm repair had mixed venous and arterial blood samples taken simultaneously from a Swan–Ganz catheter and radial line respectively. Samples were obtained before, during and after aortic cross-clamping for neutrophil count, activity (flow cytometric estimation of free radical production) and thromboxane levels (radioimmunoassay).

The following results were obtained on aortic declamping:

		Neutrophil	
	Thromboxane ($\mathrm{pg\,ml^{-1}}$)	Count ($\times 10^{9}\,\mathrm{l^{-1}}$)	Activity (MFU)
Mixed venous	764(98)*	6·7(3·1)	174(31)*
Arterial	893(114)*	3·3(1·9)*†	91(22)*†

Values are mean(s.d.). MFU, mean fluorescence units. $P < 0{\cdot}01$ *versus* *preclamp and †mixed venous values (analysis of variance)

These data demonstrate an arterial to venous difference in neutrophil count and activity across the lung following aortic aneurysm repair. Pulmonary trapping of the more activated neutrophils may explain the disproportionate lung injury after aortic aneurysm repair.

Association between colonic ischaemia and endotoxin absorption during aortic surgery

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Colonic ischaemia is a potentially fatal complication of aortic surgery. Recent studies have shown that the duration of ischaemia is highly predictive for the development of sepsis from enteric organisms, multiple system organ failure and death. Ischaemia occurring during surgery and in the early postoperative period may be detected by sigmoid tonometry. The aim of this study was to determine whether endotoxaemia occurred during and after aortic surgery, and whether this was associated with colonic ischaemic diagnosed by tonometry.

Ten patients undergoing elective infrarenal aortic surgery underwent preoperative colonoscopy and biopsy, a tonometer thereafter being inserted into the sigmoid colon. Samples were taken from the tonometer, and simultaneously venous blood for endotoxin assay (Coatest chromogenic assay; Kabi Pharmacia), immediately before and 5 min after cross-clamp application and removal, and 2, 4, 6 and 24 h after operation. Colonoscopy and biopsy were repeated after 1 week.

While endotoxin (normal mean(s.d.) level 5·83(7·92) $\mathrm{ng\,l^{-1}}$) was detected in two patients before cross-clamp application, very high levels of up to 125 $\mathrm{ng\,l^{-1}}$ were seen in five just before or immediately after clamp removal, all of whom had transient colonic ischaemia detected by tonometry, and three of whom had histological evidence of ischaemia at 1 week.

Therefore, absorption of endotoxins does occur during aortic surgery and is associated with colonic mucosal ischaemia. Whether ischaemia is the sole cause of endotoxaemia requires further evaluation.

Thrombosed popliteal aneurysm

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Since January 1988, 32 patients have presented with 43 popliteal aneurysms (PAs): 22 thrombosed and 21 non-thrombosed. Patients with thrombosed PAs were older (71 *versus* 66 years) and were more likely to have bilateral PAs ($P < 0{\cdot}05$) and serious associated cardiovascular disease ($P < 0{\cdot}05$).

Nineteen aneurysms thrombosed acutely. Twelve were treated by intra-arterial thrombolysis, which was successful in seven cases. All 12 were subsequently bypassed, as were the other seven in patients who presented with such severe ischaemia that they underwent urgent operation. One patient died and two others required major amputation. Other complications included foot drop (two), renal failure (one) and wound infection (two). Two grafts thrombosed and required re-exploration. Elective bypass was carried out in 11 patients without acutely thrombosed aneurysm. There were no significant postoperative problems.

Distortion within the aneurysm ($P < 0{\cdot}001$), large size ($P < 0{\cdot}01$) and distortion of the popliteal artery above or below the aneurysm ($P < 0{\cdot}02$) were all associated with thrombosis. Stenoses within the PA were more likely with multiple aneurysms ($P < 0{\cdot}01$) and distortion with larger aneurysms ($P < 0{\cdot}01$). After correcting for distortion within the aneurysms, none of the other variables was independently significant. The combination of distortion and diameter >3 cm was present in 87 per cent of thrombosed aneurysms.

Morbidity is high following acute thrombosis of PA. Distortion of the aneurysm appears to be a more sensitive predictor of thrombosis than size alone. The combination of distortion with an aneurysm diameter >3 cm may help to define PAs that should be bypassed electively.

Intraoperative thrombolysis in the management of thrombosed popliteal aneurysm

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Thrombosis of a popliteal aneurysm (PA) is a disaster with a high amputation rate. Acute distal thrombosis contributes to the failure of immediate bypass grafting. Preoperative thrombolysis is useful to clear the run-off in patients with a viable limb, but in severe ischaemia there is insufficient time. Intraoperative thrombolysis was used in a series of patients with this problem.

Six patients presenting with thrombosed PA required urgent surgery. At operation 100 000 units streptokinase ($n = 4$) or 3·0 mg tissue plasminogen activator ($n = 2$) was instilled over 30 min into the distal popliteal artery using a syringe driver after ligation of the aneurysm. Lysis of residual thrombus was judged using on-table angiography. Fasciotomy was performed in four cases after reconstruction.

Angiography confirmed lysis in all cases. All patients had their limbs saved and all grafts were functioning at a minimum of 3 months, confirmed by digital subtraction angiography, duplex scan and ankle indices. There was no excessive bleeding from fasciotomy sites.

Intraoperative thrombolysis is a useful adjunct to surgery for thrombosed PA. The technique encourages a more conservative approach to patients with asymptomatic aneurysm by improving the surgical results following acute thrombosis.

Lower-limb vein graft stenosis: a multivariate risk factor analysis

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Over a 4-year period 77 lower-limb vein grafts (64 *in situ*, 13 reversed) have been entered into a duplex scan surveillance programme. All stenoses were confirmed angiographically. Thirty-six stenoses developed in 22 grafts (29 per cent), 91 per cent occurring within 12 months. Stenosis was particularly common in the distal third of *in situ* grafts (64 per cent).

The following variables were studied in a multivariate analysis of risk factors for the development of stenosis: age, sex, hypertension, smoking, diabetes, grade of surgeon, inflow and outflow artery, run-off, vein size (<3 mm in diameter), distal resistance and total graft flow. Vein diameter was the only variable associated with the development of stenosis (odds ratio 7 (95 per cent confidence interval 2–34)). Seven of ten small-diameter grafts developed stenosis.

In 12 *in situ* grafts, narrowed and thickened distal segments were excised and a composite graft constructed using either arm (11) or alternative saphenous vein (one). Three of these grafts developed a stenosis at the venovenotomy but there were no distal intragraft stenoses. The overall stenosis rate in composite grafts was lower than in small-diameter vein grafts ($P = 0{\cdot}003$, Fisher's exact test).

In conclusion, a multivariate analysis has shown small vein diameter to be a significant risk factor for the development of vein graft stenosis. Possible explanations for this include an increased risk of valvulotome injury (*in situ* grafts) or high-velocity flow disturbances (reversed or *in situ* grafts). The results of this study also show that when doubt exists about a narrow distal segment of vein it should be replaced with alternative vein of greater diameter. This policy will result in a lower incidence of distal intragraft stenosis.

Prospective study of the natural history of femoropopliteal artery stenosis using duplex ultrasonography

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A foreknowledge of impending arterial occlusion and possible deterioration of ischaemia might allow their prevention by active intervention in the preocclusive stage. This could, in principle, be achieved by percutaneous transluminal angioplasty, which has been shown to have a high primary success rate in the treatment of femoral artery stenosis, a low risk, and an acceptable patency rate. The procedure is more difficult and associated with lower patency rates when occlusions are recanalized and dilated, particularly when the occlusion is long. There is, therefore, a 'window of opportunity' within which treatment is technically easier and safer. However, the length of time between the finding of a stenosis and its progression to occlusion is not known.

The aims of the present study were to determine: (1) the change in degree of femoral stenosis over time according to velocity ratio (VR) measurements determined by duplex ultrasonography; and (2) the incidence of progression from stenosis to occlusion.

Forty-three stenoses in 38 patients were studied using duplex ultrasonography to quantify the degree of stenosis. Repeat duplex examinations of the same stenoses were performed after a median of 28 weeks. Stenoses that did not occlude underwent no significant change in VR in the follow-up period. None of the stenoses with a VR <3 progressed to occlusion. Half (six of 12) of those in the VR range 3–6 and one-third (three of nine) of those in the VR range >6 occluded. It is concluded that occlusion is liable to occur as a sudden event in any stenosis with a VR $\geqslant 3$.

Smoking and platelet activity predict infrainguinal graft stenosis

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Great interest has been aroused in the prevention of myointimal hyperplasia, but patients at risk have not been defined. Prospective ($n = 46$) and retrospective ($n = 35$) groups of patients were used to study clinical risk factors (smoking, diabetes, hypertension), platelet function (plasma and intraplatelet 5-hydroxytryptamine (5-HT), β-thromboglobulin and platelet-derived growth factor (PDGF) levels, spontaneous and stimulated platelet aggregation rates), coagulation and fibrinolytic activity (fibrinogen, plasminogen, plasminogen-activator inhibitor and factors VII and VIII, and tissue plasminogen activator (tPA) activity), lipid profiles (triglycerides, total cholesterol, apoliproproteins A1 and B, high-density lipoproteins 1–3 and lipoprotein (a)) and rheological variables (whole blood and plasma viscosity) in patients who developed graft stenosis ($n = 28$) and those who did not ($n = 53$) (3 months duplex ultrasonography with or without angiographic surveillance) to a minimum follow-up of 2 years.

Results in the two groups were:

	Stenosed grafts	Non-stenosed grafts	P
Smoking	15 of 24	7 of 39	<0·001*
Plasma fibrinogen	424·6	350·0	0·004†
Plasma 5-HT	23·36	7·04	<0·001†
Platelet aggregation (adrenaline)	18·4	40·9	0·002†
Platelet aggregation (5-HT)	48·4	59·3	0·04†

*χ^2 test; †Mann–Whitney U test

Patients with polytetrafluoroethylene graft stenosis revealed greater platelet activation: plasma β-thromboglobulin and intraplatelet PDGF levels were raised significantly. No differences in incidence of diabetes or hypertension, viscosity measurements or any lipid parameters were demonstrated. Multivariate analysis showed both smoking and plasma 5-HT level to be strongly predictive of myointimal hyperplasia producing graft stenosis, but plasma fibrinogen concentration was not an independent factor. These results have defined a subgroup of patients at high risk of developing myointimal hyperplastic graft stenosis.

Human vascular smooth muscle cell culture: a model of myointimal hyperplasia

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Vascular smooth muscle cell (VSMC) proliferation is the pathophysiological basis of myointimal hyperplasia, which is the most important cause of failure after vascular surgery and angioplasty. Study of VSMC growth in culture may provide new insights into this major clinical problem.

A total of 136 samples of vascular tissue from 116 unselected patients were placed into culture between December 1990 and April 1992. Tissue was obtained from primary cardiac and peripheral bypass operations, secondary revision of graft stenosis, or organ donors. Culture was by an explant method, in standard medium supplemented with 15 per cent calf serum and antibiotic.

The overall success rate for obtaining outgrowth of cells in primary culture was 79 per cent (85 per cent if very small or inadequate samples were excluded). Some 43 per cent of cells were subcultured successfully to the third passage, comprising 37 per cent of arteries, 61 per cent of veins and 58 per cent of intimal hyperplastic stenoses, but only 6 per cent of endarterectomy specimens ($P < 0{\cdot}001$, χ^2 test).

Growth of cultured cells in response to 15 per cent calf serum is reproducible. Cell numbers were counted at 0, 3, 7, 10 and 14 days after stimulation with serum; variation (s.d.) between replicate counts within the same experiment was 6·4 per cent. Identical cells used in different experiments varied by 6·5 per cent; cells of the same lineage, but different passage number, varied by 10·6 per cent ($P > 0{\cdot}05$, F test).

Growth curves obtained from different samples within a single donor were largely identical. Growth of arterial and venous samples derived from a single donor was also similar.

Human VSMC can be successfully, simply and routinely grown in cell culture. Cell proliferation in response to 15 per cent calf serum is reproducible, and may model the *in vivo* proliferation that forms the basis of the myointimal hyperplastic lesion.

Pathogenesis of intimal hyperplasia

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It has been suggested that intimal hyperplasia occurs in regions of altered strain, particularly at anastomoses in bypass grafts. It has been shown *in vitro*, in a computer-controlled model of endothelial cells subjected to cyclical strain, that the rate of proliferation of the cells changes, as does the production of macromolecules. Adenylate cyclase controls the production of the second messenger adenosine 3′,5′-cyclic monophosphate, a process that is regulated by G proteins. Western blot analysis was used to measure changes in the immunoreactivity of inhibitory G protein following cyclical strain.

		Strain time (min)					
	Control	7·5	15	30	45	60	180
Percentage of control	100	94·5	67·8	87·7	105·2	104·1	98·3

There was no change in stimulatory G protein, but there was a transient rise in inhibitory G protein. This suggests a post-translational modification of G protein. It is concluded that the G protein–adenylate cyclase second messenger system is involved in the transduction of mechanical signals and the modification of endothelial cell function.

Endothelial regulation of smooth muscle cell proliferation and extracellular matrix formation in cultured human saphenous vein

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Current theories on the aetiology of intimal hyperplasia invoke a central role for both the endothelium and the smooth muscle cell. Organ culture of saphenous vein has recently been introduced as a model in which the interaction between these elements can be studied in human tissue.

To evaluate this model further, 40 paired segments of saphenous vein from patients undergoing arterial surgery were cultured in medium supplemented with 30 per cent fetal calf serum. Before culture the endothelium from one of the paired segments was removed by gentle abrasion. After 14 days veins were fixed and processed for electron and light microscopy. Immunocytochemical techniques were used to stain the endothelium (QBend 10), smooth muscle cells (actin), proliferating cells (proliferating cell nuclear antigen), laminin and collagen. An alcian blue stain was used to stain mucopolysaccharides in the extracellular matrix.

Intimal thickening caused by the development of a cellular subendothelial layer in cultured veins was significantly greater in the presence of endothelium (34 *versus* 9 μm; $P < 0\cdot001$, Student's paired *t* test). The cells in this layer were identified on electron microscopy as myofibroblasts with a secretory phenotype. Surrounding these cells was abundant extracellular matrix staining positively for mucopolysaccharides and laminin. Proliferating smooth muscle cells at a deeper level in the vein intima provided the new cells in the subendothelial layer.

In conclusion, the changes seen in cultured human saphenous vein (smooth muscle cell proliferation, phenotypic change and extracellular matrix formation) mimic closely the pathological changes of intimal hyperplasia. These changes are promoted by some form of messenger from the endothelium whose characterization may prove to be of therapeutic value.

Prospective randomized clinical trial of woven Dacron *versus* collagen-impregnated knitted Dacron grafts in aortoiliac surgery

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Theoretical arguments have been advanced to support the use of knitted Dacron (Du Pont) rather than woven grafts in the surgery of the aorta and iliac vessels[1]. Comparative clinical trials demonstrating superior efficacy do not exist. A prospective randomized trial inserting either woven or knitted collagen-impregnated Dacron grafts has therefore been carried out in two groups of patients with disease of the aorta and iliac vessels (115 with occlusive disease, 152 with aneurysm). At 1 year after implantation, graft patency was independently assessed by duplex ultrasonography. Equivocal findings were confirmed or refuted by intravenous digital subtraction angiography. Graft size was measured and the presence of aneurysmal or stenotic disease developing at the anastomosis assessed.

Of the patients with aneurysm, 92 were treated by tube grafts and all of these remained patent at 1 year. One of the 60 patients (32 woven, 28 knitted) who had a bifurcated graft for aneurysmal disease developed an early occlusion of one limb of the woven graft. Four of 115 grafts in patients with occlusive disease have had one limb occlude (three early, one late; two knitted, two woven). Graft occlusion eventually resulted in limb loss in two patients, while two had a successful reoperation. Only one knitted graft was removed because of infection; this patient eventually died. The mean(s.d.) operative blood loss in patients with knitted impregnated grafts was significantly lower than that in those with woven grafts (1690(1245) *versus* 1363(1172) ml, $P = 0\cdot049$). Knitted grafts had significantly dilated by a mean of 0·27 mm at 1 year ($P < 0\cdot001$), whereas woven grafts decreased slightly in diameter.

Although the sample size does not exclude a type II error, this study failed to demonstrate any improvement in graft patency or infection rate in knitted Dacron grafts. The continued use of knitted Dacron is untenable on the grounds of cost benefit.

1. Lindenauer SM, Stanley JC, Zelenock GB, Cronenwett JL, Whitehouse WM Jr, Erlandson EE. Aorto-iliac reconstruction with Dacron double velour. *J Cardiovasc Surg (Torino)* 1984; **1**: 36–42.

Platelet-derived growth factor antagonists: a possible preventive therapy for vascular graft stenosis caused by myointimal hyperplasia

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Intimal hyperplasia causes stenosis in 20 per cent of lower-limb grafts and in 20–50 per cent of peripheral and coronary angioplasties. There is as yet no effective prevention, despite several clinical trials based on results from animal models. The present experiments were therefore based on human vascular smooth muscle cells (VSMCs).

Platelet-derived growth factor (PDGF) is released from platelets, endothelial cells and VSMCs, and is known to be a major mitogen for VSMCs. The effects of the putative PDGF antagonists trapidil, indapamide and fenofibrate on human VSMC growth *in vitro* were examined.

Tissue was obtained from 14 patients undergoing primary peripheral vascular or coronary bypass surgery, or revisional surgery for graft stenosis, and from organ donors. VSMCs were cultured using an explant technique in standard medium containing 15 per cent fetal calf serum (FCS). Growth rates of subcultured VSMCs were assessed at 0, 3, 7, 10 and 14 days and the inhibitory effect of the antagonists measured. In separate experiments, inhibition of tritiated thymidine uptake in standard 15 per cent FCS-supplemented medium and serum-free medium (SFM) containing 20 ng ml^{-1} PDGF was measured.

	Mean(s.e.m.) 14-day inhibition in growth curve (%)	Mean(s.d.) inhibition of [^{3}H]thymidine uptake (%)	
		15% FCS	SFM plus PDGF
Trapidil (12 μg ml^{-1})	0(0·22)	1(5)	11(10)
Indapamide (400 μmol l^{-1})	46(3·4)*	71(9)	84(10)
Fenofibrate (100 μmol l^{-1})	51(2·4)*	41(10)	81(8)

*$P < 0\cdot001$ (Student's paired *t* test)

These results show significant inhibitory effects by both indapamide and fenofibrate, but indapamide was not effective at therapeutic levels (50 nmol l^{-1}). From the data shown, the effect is produced by inhibition of PDGF-induced growth stimulation. It is proposed that fenofibrate may prove useful for the prevention of graft restenosis.

Effect of arterial reconstruction on peripheral nerve function: implications for diabetic peripheral neuropathy

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There is evidence to implicate both metabolic and neuroischaemic mechanisms in the pathogenesis of diabetic peripheral neuropathy. To assess the relationship between tissue oxygenation and nerve function, and the potential for treatment, two related studies were performed.

Peroneal motor conduction velocity (PMCV), transcutaneous partial pressure of oxygen ($P_{\mathrm{tcO_2}}$) and skin temperature were measured on the dorsum of the foot in 34 patients with diabetes (mean age 41 (range 31–70) years; mean duration of diabetes 21 (range 9–34) years). In these patients PMCV correlated with $P_{\mathrm{tcO_2}}$ ($r = 0\cdot59$, $P < 0\cdot001$) but not with skin temperature ($r = 0\cdot16$, P not significant).

Having established this relationship, ten non-diabetic patients of mean age 59 (range 52–77) years were assessed before and after unilateral femoropopliteal bypass to study the effects on nerve function of restoring the peripheral circulation alone. Following reconstruction mean(s.d.) $P_{\mathrm{tcO_2}}$ increased from 59·3(10·7) to 70·7(7·2) mmHg ($P < 0\cdot01$) and PMCV from 42·6(6·1) to 46·7(3·2) m s^{-1} ($P < 0\cdot01$), but skin temperature was unchanged, 30·3(0·4) *versus* 30·4(1·3)°C (P not significant). There was no difference in mean(s.d.) $P_{\mathrm{tcO_2}}$ (63·2(8·8) *versus* 63·0(4·6) mmHg), PMCV (45·1(7·8) *versus* 43·4(7·2) m s^{-1}) or skin temperature (30·8(1·3) *versus* 30·2(1·2)°C) in the contralateral leg (all P not significant).

These studies provide evidence that ischaemia is associated with peripheral neuropathy in diabetes and suggest that improving tissue oxygenation can improve PMCV in humans.

Relationship between bowel ischaemia and organ impairment in elective abdominal aortic aneurysm repair

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The relationship between dysfunction of the various organs and ischaemia of the sigmoid colon was investigated in patients undergoing elective abdominal aortic aneurysm (AAA) repair.

Intramucosal acidosis is a good indicator of bowel ischaemia. In 30 patients undergoing elective AAA repair the intramucosal pH (pH$_{\mathrm{i}}$) of the sigmoid colon was measured using a silicone tonometer

(Actamed). Daily measurements were made of liver aspartate (ASAT) and alanine (ALAT) aminotransferases and of the arterial partial pressure of oxygen (P_{aO_2}). Cardiac arrhythmia and diarrhoea were observed.

In 14 of the patients, pH_i fell to <7·00 during operation. Of these 14 patients, six developed diarrhoea, compared with none of the 16 whose pH_i remained >7·00 ($P < 0·01$). Four of the 14 patients developed cardiac arrhythmia, compared with only one of the 16 whose pH_i remained >7·00 ($P = 0·15$). The postoperative rise in ASAT was higher in those whose pH_i fell to <7·00 than in those whose pH_i was >7·00: mean(s.e.m.) ASAT 426(116) *versus* 172(19) per cent ($P = 0·02$). The fall in the ratio of P_{aO_2} to fraction of inspired oxygen (F_{IO_2}) was more significant in those whose pH_i fell to <7·00 (408(23) to 177(11) mmHg) than in those whose pH_i remained >7·00 (352(32) to 260(24) mmHg, $P = 0·008$).

These results suggest that ischaemia and hypoperfusion of the sigmoid colon during AAA repair are associated with subsequent impairment of the various organs.

Aberrant growth control of human vascular smooth muscle: a possible mechanism for restenosis

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Vascular smooth muscle cell (VSMC) hyperplasia is a universal feature of healing after vascular surgery, injury and angioplasty, but can progress to restenose the lumen in 20–40 per cent of cases. It is proposed that patients who develop restenosis have aberrant VSMC growth characteristics, particularly in relation to control of growth by the physiological inhibitor, heparin.

Human VSMCs were cultured, from patients undergoing secondary operation, from graft stenosis (from the stenotic lesion) and from undiseased saphenous vein. Control samples were obtained from patients undergoing primary bypass surgery, from normal vein and artery. Growth was assessed at the third passage in subculture by the response to 15 per cent calf serum with or without 100 μg ml^{-1} heparin, counting cell numbers at 0, 3, 7, 10 and 14 days.

Cell type	Mean(s.e.m.) 14-day increase (%)	Mean(s.e.m.) 14-day heparin inhibition (%)
Stenosis ($n = 6$)	880(184)	9·9(3·8)
Vein ($n = 5$)	619(60)	4·9(4·6)
Control artery ($n = 6$)	929(119)	46·2(10·9)
Control vein ($n = 23$)	969(77)	28·5(4·4)

VSMCs from patients with restenosed lesions did not grow more rapidly in standard conditions than those from controls. Cells from patients with restenosis were significantly less sensitive to inhibition by heparin ($P < 0·001$, Mann–Whitney U test), whether derived from the stenotic lesion or from ostensibly undiseased vein.

Growth control of VSMCs from patients who develop restenosis appears to be fundamentally different from that in controls. This has important implications for the development of therapies to prevent graft and angioplasty failure, and may represent a risk factor, at the cellular level, for development of restenosis.

Hypercoagulable states and arterial thrombosis

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Hypercoagulable states (antithrombin III deficiency, protein C and S deficiencies, lupus anticoagulant) are known to predispose to venous thrombosis. Recently an association with arterial thrombosis has been suggested.

A total of 103 patients with previous arterial reconstruction of the leg were screened for abnormal thrombophilia profile. Those with a history of graft occlusion ($n = 69$) were compared with those whose graft had never failed ($n = 34$). Patient characteristics, vascular risk factors and nature of reconstruction were similar in both groups. Protein C or S deficiency was detected in 35 per cent of the group with a history of graft occlusion compared with only 12 per cent of those with a patent graft ($P < 0·02$). A difference was still observed when patients with recent (<6 months previously) graft occlusion were excluded.

To assess the effects of pre-existing hypercoagulable states on arterial reopening procedures of the leg, thrombophilia profiles have so far been performed on 40 patients before surgery or angioplasty. Abnormal profiles were detected in 12 patients, nine of whom had a protein S deficiency. Early arterial thrombosis occurred in six patients, two of whom had a preoperative hypercoagulable abnormality (one protein S deficiency, one lupus anticoagulant). There were two postoperative deaths, both in patients with protein S deficiency. Evaluation of patency rates is continuing.

Hypercoagulable states occur more frequently in patients with a history of repeated arterial thrombosis and may predispose to early postoperative arterial reocclusion and death.

Importance of vein quality for femorodistal bypass

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Autogenous vein is still regarded as the best conduit for femorodistal bypass, despite the vein graft stenosis that commonly occurs. Preoperative selection of good-quality vein should enhance outcome. In 87 patients undergoing femorodistal bypass, preoperative assessment of the long saphenous vein was conducted to measure size, anatomy, evidence of reflux and preoperative compliance. During operation vein samples were taken for histological examination, and the sites of valves and tributaries marked. Intraoperative quality control was performed using flow measurements and completion angiography. The patients were then entered into a graft surveillance programme using colour duplex ultrasonography and intra-arterial digital subtraction angiography to identify graft stenosis. Eleven patients developed graft stenosis. None was related to a tributary but one was at the site of a valve.

	No stenosis ($n = 76$)	Stenosis ($n = 11$)	P
Size			
<3 mm	27	4	n.s.*
⩾3 mm	49	7	n.s.*
Mean compliance (% per mmHg)	0·22 (0·16–0·28)	0·1 (0·08–0·14)	<0·001†
Vein incompetence	7	4	n.s.*
Histology			
Intimal hyperplasia (moderate or severe)	24	10	<0·001*
Lymphocytic infiltration (moderate or severe)	25	9	<0·005*

Values in parentheses are 95 per cent confidence intervals. *χ^2 test; Mann–Whitney U test; n.s., not significant

In conclusion, vein size, incompetence, tributaries and valves are not associated with the development of graft stenosis, whereas pre-existing morphological change and poor compliance are. Poor-quality vein at risk of developing stenosis can be identified before operation by measurement of compliance.

Subclavian steal

H. Al-Khaffaf, M. Kalra, A. Farrell and D. Charlesworth, *Withington Hospital, Manchester, UK*

A study was carried out on 58 patients who had all had carotid–subclavian bypass for the subclavian steal syndrome. Twenty-five patients had cerebral symptoms and were found to have a combination of carotid stenosis (<70 per cent) and subclavian steal. A further 20 patients had symptoms in the arm (claudication). Thirteen patients with no evidence of carotid stenosis had symptoms of dizziness, vertigo, drop attacks and transient disturbances of vision. Five of these 13 also had claudication in the ipsilateral arm. After operation (from 1 to 8 years) all patients were questioned about symptoms and underwent clinical examination, pressure measurement and duplex ultrasonography. The last two investigations were repeated after exercise.

All 13 bypasses in the latter group were patent, but all patients had retrograde flow in the vertebral artery. None of these patients had symptoms. Vertebral flow was reversed throughout the cardiac cycle in six (grade III) and in systole only in a further six (grade II). This group all reverted to grade III after exercise. In six patients pressure was measured in the subclavian artery proximal and distal to the shunt, and readings were invariably equal. This suggests an entrainment phenomenon.

In conclusion, this study throws further doubt on the origin of 'cerebellar' symptoms in patients with 'subclavian steal'.

Complications of cerebral angiography in patients with symptomatic carotid territory ischaemia screened by carotid ultrasonography

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This is the first report of the complication rate for digital subtraction angiography in patients with carotid ischaemia who have previously been screened by carotid ultrasonography so that those with normal or minimally diseased arteries do not proceed to angiography. A prospective study of 200 consecutive patients was performed for local, systemic and neurological complications following carotid angiography, defined as occurring within 72 h of the procedure.

Complications occurred in 28 patients: six (3 per cent) were local, two (1 per cent) systemic and 20 (10 per cent) neurological. The neurological complications were transient in ten (5 per cent), reversible in two (1 per cent) and permanent in eight (4 per cent). There were two deaths: one patient had an immediate stroke and died from pulmonary embolism 5 days later, and one had a severe stroke at 36 h and died from convulsions and cerebral oedema. Of the other six permanent deficits, four were mild.

The incidence of angiographic complications was greater in patients with >90 per cent stenosis and in those with persisting signs before angiography ($P < 0{\cdot}001$); it was also greater when the procedure was performed by a senior registrar rather than a consultant ($P < 0{\cdot}005$). During this same period 110 epileptic patients underwent carotid angiography for Wada tests, with three transient neurological events.

Stump pressure and cerebral blood flow

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In carotid artery surgery surgeons differ widely over the level of 'stump pressure' below which they choose to use a shunt. When the carotid is clamped, flow in the brain depends on the anatomy of the circle of Willis, the systolic pressure and the partial pressure of carbon dioxide (usually end-tidal: P_{etCO_2}). During carotid endarterectomy velocity signals (flow) were recorded in the middle cerebral artery and stump pressure, systolic pressure and P_{etCO_2} were measured. Velocities were recorded when the contralateral artery was occluded and when the internal, external and common carotid arteries were clamped. Changes in peak and mean velocities were normalized to standard pressures and P_{etCO_2}, and analysed statistically (analysis of variance).

Peak velocity in the cerebral artery was lower when there was a contralateral carotid stenosis ($P < 0{\cdot}04$). Peak and mean velocities fell with ipsilateral clamping ($P < 0{\cdot}001$) and velocity was linearly related to systolic pressure. There was no relationship between stump pressure and peak ($r = 0{\cdot}27$) or mean ($r = 0{\cdot}25$) velocity (Pearson correlation coefficient). There was a correlation when stump pressures were <30 mmHg ($P < 0{\cdot}03$).

In conclusion, ultrasonographic velocity measurements in the middle cerebral artery are more sensitive to the effects of pressure plus stenosis than stump pressure, the critical value of which is 30 mmHg.

Quality control in carotid endarterectomy: intraoperative colour-flow duplex scanning

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Operative flow measurements can be used to confirm patency after carotid endarterectomy. Intraoperative duplex ultrasonography allows the results of endarterectomy to be visualized and gives haemodynamic information.

Fifty patients had internal carotid artery (ICA) flow measured before and after endarterectomy using an operative Doppler flowmeter. The mean (95 per cent confidence interval) flow before endarterectomy was 206 (128–249) ml min^{-1} and rose to 389 (314–463) ml min^{-1} after the procedure. These measurements had no predictive value in terms of outcome.

Ten subsequent patients had completion colour-flow duplex scanning performed (Ultramark 9 HDI; Advanced Technologies Laboratories) in addition to flow measurements. Two cases of ICA stenosis were identified by duplex scanning. The first was due to a kink that caused >50 per cent narrowing. In spite of this, ICA flow increased from 300 to 441 ml min^{-1}. Arteriotomy closure was revised with a satisfactory result. The second case was due to thrombus formation causing >75 per cent stenosis; ICA flow had increased from 270 to 380 ml min^{-1}. The clot was removed and patch angioplasty performed. Duplex scanning demonstrated stenosis of the external carotid in two cases, but these were not corrected. At 1 week after operation all ten patients had patent ICAs with normal flow patterns.

Intraoperative duplex ultrasonography is a simple method of quality control and yields more information about the adequacy of carotid endarterectomy than use of a Doppler flowmeter. The long-term benefits of intervention on defects detected by duplex scanning are as yet unknown.

Haemodynamic measurements during carotid endarterectomy

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The indications for shunting in carotid surgery are controversial. Stump pressure and other haemodynamic measurements have been used to ascertain the need for a shunt. Measurements of stump pressure and internal carotid artery (ICA) flow (OpDop; SciMed) were made in 55 patients undergoing carotid endarterectomy. Bilateral transcranial Doppler ultrasonography was used to monitor ipsilateral and contralateral middle cerebral artery velocities (V_{mcaI}, V_{mcaC}). The results were analysed according to the degree of stenosis as measured by triplanar digital subtraction arteriography.

	Degree of stenosis (%)		
	71–80 ($n = 10$)	81–90 ($n = 18$)	91–99 ($n = 27$)
Stump pressure (mmHg)	46·5 (30·5–62·5)	59·6 (49·1–70 1)	44 4 (42·2–66·6)
ICA flow (ml min^{-1})	284 (163–354)	198 (121–215)	137 (101–178)
Fall in V_{mcaI} (cm s^{-1})	26 7 (13·5–48·9)	20·1 (10 2–29·8)	21·7 (17·2–26·5)
V_{mcaC} (cm s^{-1})	1·5 (−6·4 to 10·4)	−1·1 (−11·3 to 8·2)	1·3 (−10·7 to 13·3)

Values are mean (95 per cent confidence interval)

Stump pressure correlated poorly with the change in V_{mcaI} or V_{mcaC} on clamping ($r < 0{\cdot}49$ for all degrees of stenosis). ICA flow in those with 91–99 per cent stenosis was significantly lower than in those with a lesser degree of stenosis ($P < 0{\cdot}001$, Mann–Whitney U test). There was no significant difference in the fall in V_{mcaI} in the three groups. V_{mcaC} did not change on clamping.

As measured by V_{mca}, stump pressure is a poor predictor of cerebral collateral flow during clamping. In spite of >90 per cent stenosis, the ICA makes an important contribution to cerebral perfusion (137 ml min^{-1}). Stump pressure or degree of stenosis should not be used to determine the need for shunting. No additional information was derived from V_{mcaC}.

Value of serial duplex assessment of carotid artery disease

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The use of duplex scanning for the diagnosis and management of patients with carotid artery disease is well established. Considerable numbers of scans are undertaken for patients in the authors' unit both before and after operation. This study examined the benefits and implications of serial duplex ultrasonography for patients with carotid vessel disease.

All patients who underwent duplex ultrasonography in 1989 formed the cohort for the study. The scan results from preceding and subsequent years (1983–1991) were related to the patients' histories. A total of 188 patients, 119 men and 69 women of mean age 68 years, had one or more scans in 1989. For the whole period, 1041 examinations were performed (range 1–12 (median 3) per patient). Fifty-five patients underwent carotid endarterectomy, five bilateral. Those operated on had a mean of 1·4 scans before and 3·3 after surgery. Some 43 per cent of all scans were for diagnostic purposes; however, 35 per cent were undertaken after no progression of disease had been observed on two or more previous examinations. No patient within this group had endarterectomy performed or other management decision made on the information obtained by duplex ultrasonography. In 32 of 245 vessels disease progressed, and in ten cases the observed progression contributed to the decision to operate. Restenosis was found in seven cases after endarterectomy, with no action being taken for any patient. Within the study period only one new cerebrovascular accident occurred, in a patient with no significant disease within the ipsilateral vessel who had not been operated on. In 17 patients unnecessary serial assessments were made on vessels that were known to be occluded.

In conclusion, serial duplex scanning affected clinical management in only 8·1 per cent of patients. However, unnecessary duplex examinations are being performed and guidelines for the use of serial duplex ultrasonography could reduce the demand on the service by 35 per cent without any undue effect on patient care.

Fate of the external carotid artery following carotid endarterectomy

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The fate of the external carotid artery (ECA) following 'blind' endoluminal disobliteration during carotid endarterectomy was defined in 78 consecutive patients followed up at intervals of 6 months by neurological assessment and intravenous digital subtraction angiography (DSA) (mean 3·4 DSA sessions per patient). Follow-up DSA revealed nine (12 per cent) occlusions of the ECA on the operated side (three of which were known to be occluded before operation) compared with five (7 per cent) of 70 contralateral non-operated ECAs ($P = 0{\cdot}36$). Eleven patients (14 per cent) developed late neurological events (two strokes with residual disability, three with resolution and six with transient carotid territory ischaemic episodes). All patients with ECA occlusions remained asymptomatic on follow-up, and no relationship was seen between late outcome of the ECA and recurrent neurological episodes following carotid endarterectomy.

Endoluminal disobliteration of the ECA does not appear to be associated with an increased risk of ECA occlusion or late cerebrovascular events following carotid endarterectomy, and a change in practice to routine 'open' endarterectomy of the ECA is not supported.

DSA findings on follow-up	Asymptomatic	TIA	Amaurosis fugax	Stroke (recovery)	Stroke (deficit)
No significant disease	45	4	1	2	2
Plaque or ulcer	1	—	—	—	—
Stenosis (%)					
≤50	11	1	—	1	—
51–75	—	—	—	—	—
>75	1	—	—	—	—
Occluded	9	—	—	—	—
Total	67	5	1	3	2

TIA, transient ischaemic attack

Smooth muscle cell response to photodynamic therapy

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Photodynamic therapy (PDT) combines the effect of laser light and a photosensitizing drug (chromophore) to produce selective destruction of target tissue. Its main use in oncology has recently been extended to benign diseases such as vascular stenosis. The aim of this experiment was to study the uptake of the photosensitizer Photofrin (Photomedica) in vascular smooth muscle cells (SMCs), which are known to play a major role in the pathogenesis of both atherosclerosis and neointimal hyperplasia.

SMCs were cultured from the inner media of human long saphenous vein harvested for coronary artery vein bypass grafting and transferred into microtitre plates at 50 000 cells per well. Cells were incubated with Photofrin at doses of 0–100 $\mu g\,ml^{-1}$ for 48 h and then exposed to light energy of different wavelengths at green (511 nm), red (630 nm) or polychromatic wavelengths. The degree of cell destruction after treatment was assessed by a colorimetric method based on uptake of a tetrazolium salt by viable cells.

Cells were unaffected by Photofrin at 0–100 $\mu g\,ml^{-1}$ without light treatment. Treatment with light energy $\geq 3\,J\,cm^{-2}$ in the presence of Photofrin ($\geq 2\,\mu g\,ml^{-1}$) caused a mean(s.e.m.) cell destruction of 85·6(0·9) per cent ($n = 8$) regardless of wavelength. The effect was similar on cell lines from 16 individuals. Light energy without prior chromophore sensitization produced no cell damage. Exposure of the cells to light immediately after the addition of Photofrin, as well as after 48 h incubation using the same drug and light doses, suggests that the mechanism of destruction is due to activation of intracellular chromophore rather than residual chromophore in the extracellular medium.

The results suggest that arterial smooth muscle lesions could be treated successfully with PDT, given an appropriate delivery system.

Neutrophil recruitment and activation following limb revascularization

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Prolonged periods of ischaemia followed by reperfusion may result in skeletal muscle reperfusion injury and it has been suggested that neutrophils play a significant role in the pathogenesis of this injury. If this is the case, then neutrophils must first be recruited into the reperfused muscle, allowing subsequent neutrophil activation and free radical production. Thus, in a rat model of 6-h unilateral hindlimb ischaemia and 4-h reperfusion, neutrophil recruitment by reperfused muscle was assessed by measuring gastrocnemius muscle myeloperoxidase (MPO) activity (a neutrophil lysosomal enzyme, by spectrophotometric assay) and neutrophil activation quantitated by the release of neutrophil elastase into vena caval blood. Gastrocnemius muscle viability (histochemical staining) and oedema (wet:dry weight) were also assessed and indices calculated between the reperfused and contralateral normal limbs. Ten normal (no ischaemia), ten ischaemic (6-h ischaemia alone) and ten control (6-h ischaemia and 4-h reperfusion) animals were studied.

Group	Viability index	Oedema index
Normal	1·00 (1·00–1·00)	1·00 (0·98–1·01)
Ischaemia	1·00 (1·00–1·00)	1·01 (0·99–1·03)
Control	0·53 (0·33–0·61)	1·61 (1·28–1·69)

Values are median (interquartile range)

Median (interquartile range) gastrocnemius MPO activity (change in optical density per minute per gram wet weight) was normal 0·05 (0·00–0·10), ischaemia 0·075 (0·05–0·10) and control 1·07 (0·47–1·72), while elastase levels were normal 13 (0–17), ischaemia 0 (0–7) and control 23 (16–30). Thus 6-h ischaemia did not result in muscle infarction, oedema, neutrophil influx or activation. In contrast, 4-h reperfusion precipitated all of these events ($P < 0{\cdot}01$ for all parameters). These results confirm a central role for the neutrophil in postischaemic muscle dysfunction.

Smoking impairs endothelium-dependent relaxation of saphenous vein

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Smoking is associated with a decreased patency of femoropopliteal vein grafts at 12 months. Smoking, in addition to promoting arterial thrombosis, may effect intrinsic changes in the vein used for grafting. Endothelium-derived relaxing factor (EDRF), which causes vasorelaxation and inhibits platelet aggregation, could be an important factor in graft survival.

Segments of proximal saphenous vein were excised from heavy smokers (> 10 pack-years) and non-smokers undergoing varicose vein surgery or vein grafting. Specimens were sent for light and scanning electron microscopy (SEM) to confirm the presence of endothelium. Vein rings were suspended in an organ bath and the relaxations induced by bradykinin ($10^{-9}\,mol\,l^{-1}$ to $10^{-5}\,mol\,l^{-1}$) were measured after precontraction with phenylephrine ($3 \times 10^{-7}\,mol\,l^{-1}$).

Light microscopy showed no gross intimal abnormalities in the varicose veins. SEM demonstrated preservation of the endothelium. For non-smokers ($n = 6$) the maximum mean(s.d.) bradykinin-induced relaxation of varicose veins was 53·0(5·4) per cent compared with only 27·4(2·8) per cent in smokers ($n = 6$) ($P < 0{\cdot}005$). For both groups the bradykinin-induced relaxation was blocked by an inhibitor of EDRF synthesis ($10^{-4}\,mol\,l^{-1}$ nitro-L-arginine methyl ester). Preincubation of smokers' veins with $3\,mmol\,l^{-1}$ L-arginine (EDRF precursor) did not increase the relaxation. Similar bradykinin-induced relaxations were observed in non-varicose veins used for grafting.

Veins from smokers and non-smokers showed a similar relaxation (90–100 per cent) in response to sodium nitroprusside.

The EDRF-dependent bradykinin-induced relaxation of saphenous vein is reduced significantly in smokers. Impaired EDRF release in smokers could promote platelet aggregation and vasoconstriction, thereby adversely influencing graft patency.

Access to vascular surgery: an audit of the provision of services across a single health region

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Published data describing vascular surgical practice are largely from teaching centres and may not be representative of the services generally available. A study has been carried out to assess variation in the provision of vascular surgical services across a single health region in the UK.

The region consists of one teaching and seven non-teaching districts, serving a total population of over 2·5 million. Data have been collected for each health district, detailing the number of consultant episodes in 1991 for diagnostic categories related to peripheral vascular disease or aneurysm. A more detailed audit was carried out over a 3-month period in the teaching hospital and the largest district general hospital (DGH). This provided information about the route of referral, case mix and management of all vascular patients.

The results show that there are a mean of 116 consultant episodes relating to vascular diagnoses per 100 000 population per year. Six of the eight districts were within 20 per cent of this figure while the other two reported 39 and 191 per cent of this value. The lower figure was in a district that had no surgeon with a vascular interest at the time of the study; the exceptionally high figure may relate to inaccuracies in the coding of particular categories. The more detailed data showed good correlation with the summary statistics in the two districts studied. The teaching hospital and DGH serve a comparable size and cross-section of population and were referred patients of a similar case mix. Emergency referrals accounted for about 33 per cent of admissions in both centres but, at the teaching hospital, significantly more of the routine referrals were from 'out of district' (9·8 *versus* 1·6 per cent; $P < 0{\cdot}05$, χ^2 test). The teaching hospital had a higher rate of vein utilization for infrainguinal grafts (91 *versus* 41 per cent; $P < 0{\cdot}05$, χ^2 test) and carried out more carotid endarterectomies and femorodistal grafts, although <12 per cent of these were for patients from other districts.

It is concluded that the vast majority of vascular surgical patients are dealt with by hospitals in their district of residence and that the teaching hospital and DGH have a similar case mix. However, a more comprehensive vascular service appears to be available to those living in the teaching hospital district and there are few tertiary referrals. Greater access to carotid surgery and distal reconstruction would require either the provision of these services at more DGHs or tertiary referral of patients who need such treatment.

Prevention of phantom pain after major lower-limb amputation by epidural infusion of diamorphine, clonidine and bupivacaine

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Phantom limb pain may appear in up to 85 per cent of patients following amputation. There is no effective treatment. Perioperative epidural infusion of morphine and bupivacaine, alone or in combination, is effective in preventing phantom limb pain in patients with pre-existing limb pain. Serious side-effects however make such patients difficult to manage on a general ward. Clonidine has been shown to be an effective postoperative analgesic when applied epidurally. To mitigate the potentially serious side-effects of all these drugs, their combined efficacy in preventing phantom limb pain in a prospective controlled trial of 24 patients undergoing lower-limb amputation has been studied.

In the study group ($n = 13$), an epidural infusion containing 75 mg bupivacaine, 150 µg clonidine and 5 mg diamorphine was given at 1–4 ml h^{-1} for the 48 h before operation and maintained for 3–7 days after operation. The control group ($n = 11$) received opioid analgesia on demand. Pain was assessed by visual analogue score at 7 days, 6 months and 1 year. Two patients in the study group died from unrelated causes before 1-year follow-up. Urinary incontinence (four patients) and faecal incontinence (two) in the study group were the only complications. The results at 1-year follow-up are summarized.

	Study patients	Controls	*P*
Phantom pain	1	8	<0·002
Phantom limb	2	8	<0·05
Stump pain	2	6	n.s.

n.s., Not significant

It is concluded that perioperative epidural infusion of diamorphine, clonidine and bupivacaine is a safe and effective method of reducing the incidence of phantom pain after amputation.

Quality of life after vascular surgery

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Much is written about graft patency and the economics of vascular surgery. The government white paper beholds consideration of 'patients first' and a prime objective should be to study the quality of life after surgery.

A total of 396 patients with occlusive disease were studied before and after surgery, both prospectively and retrospectively, using the standard Rosser classification and scoring system.

	Before surgery	After surgery
Critical ischaemia		
Reconstruction	0·268(0·064)	0·555(0·284)
Primary amputation	0·199(0·061)	0·353(0·176)
Non-critical ischaemia		
Reconstruction	0·375(0·063)	0·736(0·248)

Values are mean(s.d.)

Thus the improvement in quality of life after reconstruction was 0·29 compared with 0·15 after amputation. All differences were significant (Student's *t* test). The biggest improvement in quality of life is after proximal procedures and angioplasty but the improvement after distal procedures is also significant. Vein grafts were better than synthetic materials in all situations below the inguinal ligament.

The quality of life improvements in the present data are comparable to those after total hip replacement, the value of which is accepted by governments and health authorities alike; the present data support the argument that reconstructive vascular surgery should also be a priority.

Prediction of outcome in infrainguinal bypass grafting

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Patient selection is of crucial importance in femoropopliteal and femorodistal bypass grafting to ensure a satisfactory clinical outcome and to avoid extensive unsuccessful surgery in patients with threat of limb loss. Altered fibrin turnover, endothelial damage and abnormal blood rheology are all associated with peripheral arterial disease; this study examines the relationship of these variables to early unsuccessful outcome in infrainguinal bypass grafting.

In 80 patients who underwent infrainguinal bypass grafting at two vascular surgical units, preoperative haematological variables, together with blood viscosity, markers of fibrin turnover (fibrinogen and cross-linked fibrin degradation products: FDPs) and markers of endothelial damage (von Willebrand factor: vWF) have been correlated with a poor outcome within 8 weeks of surgery, defined as death, graft occlusion or persisting symptoms leading to amputation.

In 18 patients with a poor outcome (11 occlusions, five deaths, two persisting symptoms), preoperative platelet count, white cell count, blood viscosity, FDPs and vWF were all significantly higher than in successful grafts ($P = 0{\cdot}05$, Mann–Whitney *U* test). Poor outcome was more common in distal popliteal and femorocrural grafts, and in those carried out for limb threat and distal sepsis. Mean age and angiographic score were, however, similar in both groups, as were the proportions of diabetics and smokers.

These results suggest that the preoperative evaluation of these variables may assist the vascular surgeon in the identification of patients unlikely to benefit from infrainguinal grafting. Studies are continuing to develop a predictive index for poor outcome.

A 2-year follow-up of femoropopliteal bypass using bovine carotid biograft

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Although long saphenous vein remains the conduit of choice for proximal femoropopliteal bypass, there are occasions when it is either deemed unsuitable or preserved for possible more distal bypass. Reported here are the 2-year results of the St Jude biopolymeric graft, which has high tensile strength and a reduced thrombogenicity as a result of its negatively charged wall.

A total of 61 patients had 64 proximal femoropopliteal grafts implanted between July 1988 and July 1990 for symptoms of disabling claudication, rest pain and/or gangrene. All were considered suitable for proximal bypass after measurement of arterial pressure and arteriography. The mean preoperative ankle:brachial pressure index was 0·53 (range 0·16–0·91) with 14 limbs having three-vessel, 32 limbs two-vessel and 18 limbs one-vessel run-off.

All patients studied are now at least 2 (range 2–4) years after implant. To date primary patency has been obtained in 42 grafts, there are 21 occlusions and one has been lost to follow-up. Eight patients have died, five of whom had patent grafts at the last follow-up visit. Cumulative patency rates over the follow-up period have been 72, 70, 70, 70 and 70 per cent for the periods 6 months and 1, 2, 3 and 4 years respectively with the at-risk population for each of these periods being 46, 40·5, 33·5, 19 and 3·5 respectively. Surprisingly, to date, no occlusions have occurred in grafts that have remained patent for 1 year.

The patency rates achieved with this graft are at least as good as those obtained with polytetrafluoroethylene (PTFE). No long-term complications have been seen with this graft and in particular no clinical evidence of aneurysm formation has been seen although at present the patent group are undergoing duplex scanning to check the integrity of the grafts. The satisfactory patency rates and lack of longer term complications plus the fact that graft function can be monitored using the duplex scanner suggest that this biograft may be worth further evaluation as an alternative to PTFE.

Above-knee femoropopliteal bypass and the consequences of graft failure

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A total of 290 femoral to above-knee popliteal artery bypasses were performed between January 1983 and September 1991. Polytetrafluoroethylene (PTFE) grafts were used in 113 cases (39 per cent) and vein grafts in 177 (61 per cent) (146 reversed, 31 *in situ*). Grafts were followed for a median of 20 months. The 2-, 4- and 6-year patency rates for vein and PTFE grafts were 70, 62 and 57 per cent compared with 58, 46 and 41 per cent respectively ($P = 0·2$). The corresponding 2-, 4- and 6-year limb salvage rates were 82, 78 and 62 per cent compared with 75, 64 and 58 per cent ($P = 0·6$). Some 99 grafts occluded during follow-up (45 PTFE, 54 vein). Major amputation was required in 63 limbs: below-knee in 37 (59 per cent) and above-knee in 26 (41 per cent). Final healing at the below-knee level was achieved in 23 of 35 (66 per cent) and 14 of 28 (50 per cent) amputation stumps for vein and PTFE respectively ($P = 0·11$, χ^2 test). The trend for superior patency of autogenous vein grafts to the above-knee popliteal artery has again been demonstrated, although no difference in the final amputation level was shown. The ultimate fate of the limb should be considered when evaluating bypass procedures.

Arm vein: the conduit of choice in the absence of long saphenous vein

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The long saphenous vein (LSV) is widely regarded as the bypass conduit of choice for below-knee femoropopliteal and femorocrural bypass. Many studies have shown that excellent long-term patency may be achieved using reversed or *in situ* LSV, with 5-year patency rates of 60–70 per cent in the majority of published studies. By comparison the long-term results with prosthetic grafts are poor, with 5-year patency rates around 30–40 per cent. While a number of studies have examined arm vein in isolation, few have performed a direct comparison between the results of LSV and those of arm vein used for femorocrural bypass. To compare the results of LSV with those of arm vein bypass, 208 femorocrural reconstructions performed between 1985 and 1991 were studied. The LSV was used in 150 bypasses and arm vein, most commonly the cephalic vein, in 58. There were no significant differences between the LSV and arm vein groups for hypertension (32 *versus* 26 per cent), diabetes (29 *versus* 18 per cent), ischaemic heart disease (15 *versus* 6 per cent), previous stroke (12 *versus* 9 per cent) or smoking status (60 *versus* 55 per cent). Mean follow-up was 44·5 months. The cumulative patency rate in the LSV group at 44 months was 63 per cent compared with 72 per cent in the arm vein group ($P = 0·14$). The cumulative limb salvage rate over the same period was 97 per cent for arm vein and 77 per cent for LSV bypass ($P = 0·62$). It is concluded that the results of using arm vein for femorocrural bypass are at least as good as those achieved with LSV, and that arm vein should be used for distal bypass when saphenous vein is not available.

Prospective trial of low molecular weight heparin *versus* aspirin and dipyridamole in femoropopliteal bypass grafts

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Thrombosis, often associated with the luminal changes of intimal hyperplasia, is the most common cause of graft failure within the first year of surgery. Recent evidence suggests that the benefits of aspirin plus dipyridamole on graft survival are limited to its antithrombotic effect in humans. Low molecular weight heparin (LMWH) has the potential advantage of not only a superior antithrombotic activity but also a potent antiproliferative effect on smooth muscle cells, thereby limiting the damaging process of intimal hyperplasia.

In a prospective multicentre trial, 200 patients undergoing femoropopliteal bypass grafting were randomized to receive either a daily injection of 2500 units LMWH or 300 mg aspirin combined with 100 mg dipyridamole at 8-h intervals, for 3 months. The groups were matched for age, sex, smoking, hyperlipidaemia, indication for surgery (claudication or salvage), graft type, level of anastomosis and run-off. All patients were followed for 1 year.

Overall, LMWH decreased the rate of graft failure throughout the trial compared with aspirin–dipyridamole: at 3 months, 6·5 *versus* 10·8 per cent (P not significant); at 6 months, 16·4 *versus* 39·7 per cent ($P = 0·03$); and at 1 year, 30 *versus* 57 per cent ($P = 0·01$). The main benefit of LMWH was seen in patients with critical ischaemia. The proportion of patients with patent grafts at 6 months (LMWH *versus* aspirin–dipyridamole) was 83 *versus* 59 per cent, relative risk 1·41 (95 per cent confidence interval 1·07–1·85) ($P = 0·03$), with a highly significant increase of graft patency persisting at 1 year (79 *versus* 45 per cent, relative risk 1·76 (95 per cent confidence interval 1·24–2·49), $P = 0·003$). Analysis of graft type revealed that LMWH significantly outperformed aspirin–dipyridamole in maintaining prosthetic graft patency ($P = 0·02$). This difference was accentuated when the most thrombogenic (Dacron; Du Pont) grafts were used ($P = 0·003$).

It is concluded that LMWH is a safe and highly effective adjuvant therapy to peripheral vascular grafting, and is significantly superior to aspirin–dipyridamole in both salvage and prosthetic graft surgery.

Haemodynamic measurements as predictors of early outcome after infrainguinal vein bypass

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In the presence of an adequate inflow, the bypass conduit and distal vessels are two factors important in predicting the early (within 30 days) outcome of bypass surgery. In 100 femorodistal reconstructions, flow measurements and graft resistance were obtained. The capacity ratio of the vein graft was calculated using flow measurements performed before insertion of the distal anastomosis and after administration of 30 mg papaverine hydrochloride.

	Resistance (p.r.u.)		
	Success ($n = 88$)	Failure ($n = 12$)	P*
Popliteal	0·40 (0·36–0·44)	0·97 (0·87–1·07)	<0·001
Single calf vessel	0·58 (0·52–0·64)	1·09 (0·65–1·43)	0·003

Values are mean (95 per cent confidence interval). p.r.u., Peripheral resistance units. *Mann–Whitney U test

Grafts in three patients in the failure group, with a measured resistance after papaverine <0·9 p.r.u., failed because of a conduit problem. If the resistance measurements had been used in conjunction with the capacity ratio, the results below can be obtained with regard to graft failure.

	Resistance >1 p.r.u.	Resistance >0·9 p.r.u.	Resistance >0·9 p.r.u. and capacity ratio <10%
Sensitivity (%)	58	75	92
Specificity (%)	99	97	97
Accuracy (%)	94	94	97

Haemodynamic measurements are a useful indicator of outcome provided that some assessment of conduit function is included.

Minimally invasive femorodistal vein bypass

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Angioscopy has the potential for use in vein graft preparation, allowing valve lysis and identification of tributaries under direct vision. Before the present study, angioscopic valve lysis had been performed in 21 fully mobilized vein grafts. Twelve patients underwent minimally invasive angioscopic femorodistal bypass using either an Olympus or Storz system. Some 61 valves were destroyed under direct vision using a flexible valvulotome. A total of 68 tributaries were identified by the angioscope; a small stab incision was made and the tributary then ligated. No evidence of fistula was found by subsequent duplex scanning and arteriography. One patient had a retained valve cusp that required reoperation at 1 week. One graft failed at 6 days secondary to an outflow stenosis. The mean volume of irrigating fluid used was 600 (range 350–1700) ml. The mean (range) hospital stay after surgery was 5·2 (4·0–7·0) days compared with 9·5 (8·0–12·0) days in a historical group of 30 patients ($P < 0{\cdot}001$). Early experience suggests that hospital stay may be significantly reduced by 'minimally invasive' *in situ* femorodistal bypass.

Outpatient clinic follow-up after arterial reconstruction

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By tradition, many surgeons review patients regularly in the long term after arterial reconstruction. However, Harris[1] has recommended that patients should be seen only once in the clinic after operation and, thereafter, up to 1 year only for graft imaging if appropriate. The authors have for several years pursued a policy of minimal clinical follow-up and the present study examined the results and views of patients on this approach (before introduction of duplex surveillance).

All patients who had grafts for occlusive disease of arteries to the lower limbs during 1987 to 1989 were reviewed, using only case notes if graft failure, limb loss or death was documented, and by using structured interview and examination for the remainder. There were 172 patients (116 men) aged 40–95 (median 71) years undergoing 179 procedures: 48 aortoiliofemoral grafts and 131 infrainguinal reconstructions. During the review period of 30–66 months, 100 patients (58 per cent) lost limbs or died.

Of the patients available for review, 49 (86 per cent) described continuing symptomatic improvement. A median of 1 (range 0–6) postoperative appointment was received by this group. Thirty-nine patients (68 per cent) found one follow-up appointment helpful for reassurance and 36 (63 per cent) considered further regular hospital review unnecessary. A total of 44 of 55 grafts (80 per cent) assessed by clinical examination and Doppler ultrasonography were patent; however, 14 patients (25 per cent) had recommenced smoking.

This study suggests a policy of minimal clinic follow-up is acceptable to the majority of patients. Patients are educated to attend immediately in the event of ischaemic symptoms. The authors believe that simple clinic follow-up confers little benefit in the prevention of graft occlusion.

1. Harris PL. Follow-up after reconstructive arterial surgery. *Eur J Vasc Surg* 1991; 5: 369–73.

Chronic critical leg ischaemia must be redefined

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The European Consensus Document[1] defines critical limb ischaemia in non-diabetic patients as rest pain or tissue necrosis (ulceration or gangrene) with an ankle systolic pressure <50 mmHg. To determine the clinical relevance of this definition, the present study reviewed 154 ischaemic limbs in 124 non-diabetic patients who presented with rest pain, tissue necrosis or a combination of these. The median age was 73 (range 48–90) years, with a male:female ratio of 2·3:1.

Only 49 per cent of limbs fulfilled the current definition (ankle systolic pressure <50 mmHg); 51 per cent had a pressure ⩾50 mmHg and were thus not defined as critically ischaemic. Limb salvage and mortality rates of limbs with an ankle systolic pressure <50 mmHg were compared with those of limbs with a pressure ⩾50 mmHg. The results are shown below, expressed as percentages and actuarial survival rates as determined by life-table analysis.

Ankle systolic pressure (mmHg)	No.	Tissue necrosis (%)	Limb salvage rate at 9 months (%)	Mortality rate at 24 months (%)
<50	76	40	72·7	45·9
⩾50	78	50	74·5	21·9

There are no significant differences between any of the categories (χ^2 or log rank test). The results show that an ankle systolic pressure <50 mmHg does not predict the presentation or outcome of patients with severe limb ischaemia. The current definition of critical limb ischaemia based on an arbitrary ankle systolic pressure of <50 mmHg is inadequate and needs to be revised.

1. Dormandy J, ed. *European Consensus Document on Critical Limb Ischaemia.* Berlin: Springer-Verlag, 1989.

Polytetrafluoroethylene grafts and vein collars: clinical and histological evidence from intimal hyperplasia

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Since 1984, 71 >60-cm polytetrafluoroethylene (PTFE) grafts to crural arteries (21 per cent of all crural grafts) have been performed, giving primary and assisted patency rates of 46 and 61 per cent at 1 year and 33 and 49 per cent at 3 years (i.e. 25 per cent worse than similar vein grafts). All grafts were inserted for critical ischaemia (37 per cent rest pain, pressure <40 mmHg; 37 per cent rest pain, ulceration or gangrene; 26 per cent concomitant minor amputations) and irreversible graft failure led to amputation in 97 per cent of patients. Technical advantages alone do not explain these better long-term results. There is consistently less distortion of the artery using the vein collar and the exponential increase in distortion with decreasing diameter means that these changes become critical in crural vessels. Since vein wall is anisotropic, the collar optimizes vein compliance. As a result of these studies the configuration of the collar has been altered to improve its haemodynamics.

At least one-third of prosthetic grafts occlude because of anastomotic intimal hyperplasia in the recipient artery. Ten venous collars have been retrieved following amputation; all had stenosis at the PTFE–collar anastomosis but the recipient artery was spared. Histological examination confirmed intimal hyperplasia. Thrombolysis has shown one 90 per cent stenosis at the graft–collar anastomosis but a normal recipient artery in one patient; in another patient an undamaged artery has been shown after graft occlusion. It is concluded that experimental data and clinical experience show that a vein collar has a sufficient diameter and compliance to minimize and alter the site of intimal hyperplasia and protect the recipient crural artery.

Arteriography as an outpatient procedure

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Diagnostic arteriography was previously performed using in-hospital beds and involved an overnight stay. Recently, patients have required observation for 2–4 h following angiography with 4- or 5-Fr catheters.

Although this procedure is safe, problems can occur, particularly in the elderly.

Over the past 2 years, 500 patients have been studied using a 3-Fr catheter set with flow rates up to 6 ml s^{-1} and digital subtraction angiography (DSA). The 3-Fr catheters have just over half the cross-sectional area of a 4-Fr catheter measuring 1 mm in diameter. Following catheter withdrawal, pressure was applied to the puncture site for 5 min. The patient remained supine for 30 min and was then allowed home. The main indications were suspected renal or peripheral vascular disease and graft surveillance.

The use of the catheter set was straightforward with the advantage that there was no difficulty introducing the catheter into scarred groins or synthetic grafts. There were no major technical problems at the flow rates used. Image quality was excellent throughout; no patient required further diagnostic angiography. Apart from one minor bruise there was no immediate or late complication. All outpatients were allowed home 1 h after the procedure.

In addition, 15 inpatients who underwent anticoagulation have been studied. All were receiving warfarin, with a prothrombin time greater than twice normal. Puncture-site pressure was applied for 10 min and patients mobilized 1 h after the procedure. None developed haematoma or other problem.

It is concluded that, in centres where DSA is available, all renal and peripheral non-selective arteriography can be performed safely as a true outpatient procedure using 3-Fr catheters.

Radionuclide assessment of peripheral arterial disease using ^{99m}Tc-labelled methoxyisobutylisonitrile

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Thallium-201 has been used to investigate peripheral arterial disease; it has provided useful information about muscle blood flow but has not been widely adopted because of poor spatial resolution. A new agent, ^{99m}Tc-labelled methoxyisobutylisonitrile (MIBI) is used to assess muscle perfusion; this label enables better spatial resolution. The technique has been described in detail elsewhere[1].

A total of 17 patients with angiographically proven peripheral arterial disease and 11 controls were studied. Exercise calf muscle perfusion was significantly reduced in patients with peripheral arterial disease ($P < 10^{-6}$) with a sensitivity of 94 per cent and specificity of 95 per cent for diagnosis of disease. There were significant correlations in disease severity as assessed with ^{99m}Tc-MIBI and angiography ($r = 0{\cdot}54$, $P < 0{\cdot}0001$) and Doppler ankle:brachial pressures ($r = 0{\cdot}64$, $P < 0{\cdot}002$). Muscle uptake increased after successful angioplasty in two patients. Simultaneous radionuclide angiography allowed diagnosis of a 2-cm popliteal aneurysm in one patient. Emission tomography allows evaluation of regional variations in perfusion of the calf.

Unlike Doppler measurements, the present technique benefits from assessing muscle perfusion at the cellular level. It successfully diagnoses and evaluates peripheral arterial disease and is likely to be of most benefit to patients such as diabetics, in whom Doppler studies may be inaccurate.

1. Miles KA, Barber RW, Wraight EP, Cooper M, Appleton DS. Leg muscle scintigraphy with ^{99}Tc^{m}-MIBI in the assessment of peripheral vascular (arterial) disease. *Nucl Med Commun* 1992; 13: 593–603.

Early results of a gentle exercise class for intermittent claudication

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Exercise is believed to increase walking distances in patients with intermittent claudication, but intensive exercise classes remain unpopular, despite some encouraging published results. This may be due to cost, fears of safety (systemic effects of claudication) or poor compliance. The use of a less demanding exercise regimen has therefore been investigated.

Stable claudicants attended an exercise class run by a physiotherapist, for 2 h, one morning per week for 6 weeks. Maximum walking distance was measured at the beginning and end of this period. Forty-two of 45 claudicants increased maximum walking distance, by a mean of 151 per cent, including nine who were stopped after 15 min pain-free walking at the second assessment. The median (range) maximum walking distance increased from 161 (37–606) m to 385 (57–1207) m ($P < 0{\cdot}001$, Wilcoxon signed rank test). To date, 18 patients have been reassessed at 6 months and increased maximum walking distance has been maintained in 15 ($P < 0{\cdot}001$, Wilcoxon signed rank test).

These encouraging results are comparable to those achieved by more intensive regimens. A controlled trial investigating the local and systemic effects of gentle and intensive exercise in claudicants is planned, but it is suggested that a gentle exercise class is safe and effective in the management of intermittent claudication.

Haematological parameters and prediction of bleeding during peripheral thrombolysis

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All thrombolytic agents induce, to a variable extent, a systemic fibrinolytic state that may play a role in causing haemorrhagic complications. This study investigated whether patients who bleed during thrombolysis can be distinguished from those who do not by comparing haematological indices from 19 patients who suffered major haemorrhagic complications during thrombolysis with results from 160 similarly treated patients in whom bleeding did not occur.

Patients received one of three different thrombolytic agents: streptokinase, Eminase (Smith Beecham) or recombinant tissue plasminogen activator, by either local or systemic infusion. Plasma fibrinogen (Fib.), plasminogen (Plas.), fibrin(ogen) degradation products (FDPs), cross-linked fibrin degradation products (XDPs), euglobulin clot lysis time (ELT), α_2-antiplasmin (α_2-AP) and coagulation times were measured at two timepoints before lysis (sample 1) and after 16–20 h therapy (sample 2).

Sample	Fib. (g/l)	Plas. (%)	FDPs (mg/l)	XDPs (µg/l)	ELT (s)	α_2-AP (%)	INR	APTT (s)	TCT (s)
1									
Bleeding	3·8	95	<8	<250	243	86	1·1	41	16
No bleeding	4·5	96	<8	<250	255	93	1·1	45	17
2									
Bleeding	2·8	49	60	500	30	30	1·3	41	21
No bleeding	2·8	62	40	1000	35	30	1·2	47	23

Values are mean or median, as appropriate. INR, international normalized ratio; APTT, activated partial thromboplastin time; TCT, thrombin clotting time

Haematological and fibrinolytic parameters in patients who suffer haemorrhagic complications during thrombolysis do not differ significantly from those in patients who do not. Monitoring of these fibrinolytic parameters is of no benefit in predicting haemorrhagic complications and the inability to measure these parameters should not therefore prevent the use of peripheral thrombolysis.

The von Willebrand factor in atherosclerotic vascular disease

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Myocardial infarction and peripheral vascular disease are varieties of atherosclerosis in which endothelial injury and thrombosis are important. The von Willebrand factor antigen (vWFAg), released by damaged endothelium, mediates platelet adhesion and aggregation, and circulating levels are increased by the risk factors for atherosclerosis.

vWFAg (using an enzyme-linked immunosorbent assay) and risk factors were measured in non-diabetic patients with peripheral vascular disease, patients 6 weeks after myocardial infarction, and asymptomatic hospital staff and attenders at endoscopy, hernia and varicose vein clinics as controls; all were controlled for smoking, age and sex. Data were analysed by the Mann–Whitney *U* test and analysis of variance.

Mean(s.d.) serum vWFAg in 111 patients with peripheral vascular disease was 132(39) ($P < 0{\cdot}0001$) compared with 102(36) units dl^{-1} in controls and 140(36) units dl^{-1} in 63 patients following myocardial infarction ($P < 0{\cdot}0002$). These differences were influenced by hypertension (blood pressure >140/90 mmHg) and hyperlipidaemia (cholesterol >7 mmol l^{-1}) but not cigarette smoking, glucose or fibrinogen.

In 61 patients with peripheral vascular disease and either hypertension ($n = 50$) and/or hypercholesterolaemia ($n = 28$), mean(s.d.) vWFAg was 137(33) units dl^{-1}, no higher than in 50 patients with peripheral vascular disease without these risk factors (145(40) units dl^{-1}). However, in ischaemic heart disease, mean(s.d.) vWFAg in 24 patients with these risk factors (hypercholesterolaemia $n = 15$, hypertension $n = 9$) was 154(38) units dl^{-1}, compared with lower levels

(120(34) units dl^{-1}) in 39 patients without these risk factors ($P < 0{\cdot}0015$).

The level of vWFAg was increased irrespective of hypertension and/or hypercholesterolaemia in patients with peripheral vascular disease but in those with ischaemic heart disease it was significantly higher with these risk factors. A different pathophysiology may be involved in a proportion of survivors of myocardial infarction.

Tissue factor is more relevant to arterial haemorrhage than to thrombosis

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Tissue factor is a cellular protein that initiates the extrinsic coagulation pathway. *In vitro* experiments on cultured endothelial cells have shown that endotoxin and other inflammatory mediators can induce the production of tissue factor, and this may be the first step in intravascular thrombosis.

Tissue factor *in vivo* in the thoracic aorta of male New Zealand White rabbits given intravenous endotoxin (0·05 mg kg^{-1}) was studied. The aorta was harvested under general anaesthesia, divided longitudinally and placed in an assembly exposing the endothelial surface. A functional assay was performed with human coagulation factors VII and X which relied on a colorimetric change proportional to the concentration of tissue factor present. The median (range) concentration of tissue factor in normal rabbits ($n = 10$) was 0·0 (0·0–0·6) units l^{-1}, and in rabbits treated with endotoxin was 0·0 (0·0–0·3) units l^{-1}. There was no difference between normal and treated rabbits, indicating no increase in production of tissue factor in the endothelium of the treated group ($P = 0{\cdot}46$, Mann–Whitney U test).

In situ hybridization was performed to detect messenger RNA responsible for tissue factor production. The RNA gene probe was transcribed from human tissue factor complementary DNA. Specimens of thoracic aorta from normal and endotoxin-treated rabbits were assessed. Rabbit monocytes treated with endotoxin were used as a positive control. Tissue factor messenger RNA was not detected in the endothelium or adventitia of normal rabbits ($n = 3$); nor was it detected in the endothelium of animals treated with endotoxin ($n = 3$). However, messenger RNA for tissue factor was detected in the adventitia of the endotoxin-treated animals.

Endotoxin increases the production of tissue factor in the adventitia, where it may have an important role in the arrest of haemorrhage from damaged blood vessels. Tissue factor was not produced by the endothelium in response to endotoxin, and may not indicate thrombosis, but the role of monocytes that are capable of manufacturing tissue factor remains to be determined.

Thrombolysis of occluded infrainguinal vein grafts before operative intervention

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Long saphenous vein graft occlusion results in limb-threatening ischaemia. Despite vein graft surveillance the first presentation may be with occlusion. Revascularization is facilitated if the aetiology of the occlusion is known before operation. A consecutive series of 31 patients presenting 7–19 days after occlusion of an infrainguinal long saphenous vein graft initially inserted for critical ischaemia have been prospectively studied to assess the outcome of thrombolysis with intraluminal recombinant tissue plasminogen activator (tPA).

Catheter placement failed in three patients but thrombolysis was successful in 28 within 24 h, revealing an inflow problem in five, graft stenosis in eight, distal anastomotic stenosis in five and distal disease progression in seven. Three patients appeared to have no technical problem and received anticoagulation.

Successful revascularization was achieved in 18 patients (58 per cent) by operative or radiological intervention directed at the aetiology of the occlusion. This compares favourably with 43 per cent of patients in a retrospective series who did not receive tPA before surgery. Thrombolysis-related complications were confined to a false femoral aneurysm, a retroperitoneal haemorrhage and rhabdomyolysis-related renal failure.

The results suggest that intra-arterial thrombolysis with tPA is a valuable preliminary investigation to determine the aetiology of long saphenous vein graft failure allowing directed intervention. A prospective randomized study is now required.

Tissue-cultured graft as an ideal endothelial cell attachment substrate

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The concept of endothelial cell seeding to reduce graft thrombogenicity has received much attention, but in practice has yielded little success to date. This may be the result of using unsuitable synthetic substrates or attachment factors that provide only temporary benefit. An alternative approach is presented in which the substrate for endothelial cell attachment more closely resembles the *in vivo* situation.

Vascular cell types were isolated from human saphenous vein. Smooth muscle cells (SMCs) were harvested using an explant technique and successfully grown to fourth passage, i.e. an 81-fold increase in cell number. Endothelial cells were harvested by enzymatic cleavage and, using a medium containing growth factors, heparin and human serum, were subsequently cultured to third passage, i.e. a 27-fold increase in cell number. The cultured endothelium retained biochemical function as demonstrated by plasminogen activator production and inhibition of platelet aggregation. Acid-solubilized type I collagen was recovered from minced tendon by a two-step process and its purity assessed by sodium dodecylsulphate polyacrylamide gel electrophoresis. The collagen was then neutralized in a gel containing the human SMC, culture media and pooled human serum. Over a period of 2 weeks the collagen was organized by the SMC into a fibrous tissue-like structure. Under scanning electron microscopy this structure closely resembled the subendothelium of vein. Human saphenous vein endothelial cells were then seeded supraconfluently ($5–7 \times 10^4\ \mathrm{cm}^{-2}$) without attachment factors on to the collagen matrix. After 1 week in culture the endothelium was shown to be organized into a smooth pavemented confluent monolayer with tight junctions. Histological analysis showed the endothelial monolayer to be well incorporated on the surface of the collagen matrix.

In conclusion, a cell-populated collagenous matrix appears to provide an ideal surface for endothelial seeding.

Risk factors for recurrence in patients with healed leg ulceration

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Compression stockings are prescribed to patients with newly healed venous ulcers, yet little is known of their effectiveness in preventing ulcer recurrence.

Patients with recently healed ulcers were assessed for use of stockings. Those suitable for stockings were randomized to one of two class II stockings (Duomed *versus* Scholl) and followed for up to 18 months. In all, 189 patients were entered in the study, of whom 167 were considered to be suitable for stockings and were randomized accordingly. The remainder either required 'made-to-measure' stockings (five patients) or could not tolerate stockings at all (17). The overall cumulative recurrence rate was 11 per cent at 3 months, 25 per cent at 12 months and 29 per cent at 18 months. The recurrence rate was 34 per cent in patients not given stockings compared with 25 per cent in those given stockings ($P = 0{\cdot}004$). The randomized groups showed no significant difference in cumulative recurrence rate (22 *versus* 28 per cent, $P = 0{\cdot}88$).

Factors that predicted ulcer recurrence were previous ulcer size $> 10\ \mathrm{cm}^2$ (relative risk 2·18 (95 per cent confidence interval (c.i.) 1·15–4·14), $P = 0{\cdot}002$), failing to wear support stockings all day (relative risk 4·57 (95 per cent c.i. 1·80–11·63), $P = 0{\cdot}002$) and failing to wear stockings every day (relative risk 2·73 (95 per cent c.i. 1·06–7·05), $P = 0{\cdot}031$). Factors not significantly associated with recurrence included ankle:brachial pressure index $< 0{\cdot}9$, hypertension and diabetes.

This study has indicated the importance of stockings in the prevention of leg ulcer recurrence.

Foot volumetry and duplex ultrasonography in patients with recurrent venous ulceration after subfascial ligation of perforating veins

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Forty-three consecutive patients undergoing subfascial ligation of perforators as part of surgery for recurrent venous ulceration underwent preoperative foot volumetry and postoperative duplex ultrasonography. Patients were followed for a median of 66 (range 18–144) months. Of nine patients developing recurrent ulceration, six had femoral vein incompetence (FVI) and all had popliteal vein incompetence (PVI). Of the 34 patients remaining ulcer-free, five had FVI and one PVI, giving FVI and PVI positive predictive values for recurrent ulceration of 54 and 90 per cent respectively. Patients with saphenofemoral but not saphenopopliteal incompetence were also more likely to suffer recurrence. Foot volumetry with tourniquet occlusion of superficial veins showed the median (range) expulsion fraction of patients with recurrent ulcer disease to be 0·8 (0·6–2·3) per cent, compared with 1·4 (0·4–2·9) per cent for those without ($P = 0{\cdot}025$); the median (range) half-refilling time of patients with recurrent ulcer was 1·5 (0·5–5·5) s, compared with 5·0 (0·5–23·0) s for those without ($P < 0{\cdot}01$). Deep venous incompetence, particularly of the popliteal segment, as shown by duplex scanning and foot volumetry is therefore associated with a high incidence of recurrent ulceration after subfascial ligation. It is suggested that this group of patients be treated conservatively or considered for reconstructive venous surgery.

Infrapopliteal angioplasty: a safe and successful procedure

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During a 65-month period, 40 infrapopliteal percutaneous transluminal angioplasties (PTAs) have been performed in 38 patients. Thirty (79 per cent) of the patients were men, 17 (45 per cent) were diabetic and 11 (29 per cent) admitted to continued smoking. Of the procedures, 20 (50 per cent) were for intermittent claudication, six (15 per cent) for rest pain alone, four (10 per cent) for ulceration and ten (25 per cent) for gangrene. A total of 21 procedures (52 per cent) were to infrapopliteal vessels alone, 16 (40 per cent) to infrapopliteal vessels plus one other arterial segment and three (8 per cent) to infrapopliteal vessels plus two other arterial segments. Some 17 (42 per cent) of the infrapopliteal procedures were to the anterior tibial artery alone, eight (20 per cent) to the tibioperoneal trunk, four (10 per cent) to the posterior tibial artery, seven (18 per cent) to the peroneal artery and four (10 per cent) to multiple infrapopliteal vessels. There were two complications (5 per cent), both distal emboli that were aspirated percutaneously. There were no deaths or limb losses related to the angioplasty procedure.

There was one technical failure; the remaining 39 limbs (98 per cent) were clinically improved by 24 h and this improvement was sustained at 3 months in 36 (90 per cent). Ten of the 14 procedures performed for ulceration or gangrene resulted in healing with only minor surgical intervention. The actuarial symptomatic patency rate at 2 years was 60 per cent; the haemodynamic patency rate was 68 per cent assessed on the basis of further arteriograms and/or ankle pressures in the angioplastied vessel. The 2-year actuarial haemodynamic patency rate was not significantly different in limbs that had undergone PTA of the infrapopliteal vessel alone (63 per cent) or in combination with another arterial segment (75 per cent) ($P = 0{\cdot}39$, log rank test). The 2-year actuarial limb salvage rate for the 20 patients with critical ischaemia was 79 per cent.

In conclusion, PTA of the infrapopliteal vessels can be performed with a low complication rate (5 per cent) and produce a symptomatic improvement in 60 per cent of all limbs at 2 years. In critically ischaemic limbs, infrapopliteal vessel angioplasty can result in a 2-year limb salvage rate of 79 per cent and lead to healing in 71 per cent of limbs with ulceration or gangrene.

Percutaneous transluminal angioplasty and the critically ischaemic limb

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During the 41-month period June 1988 to October 1991, 233 limbs presented with critical ischaemia; 55 (24 per cent) were treated by percutaneous transluminal angioplasty (PTA) alone and five (2 per cent) by a combination of PTA and surgery (three iliac PTAs before femorodistal bypass, two iliac PTAs before iliofemoral crossover bypass). The 55 limbs treated by PTA alone were in 53 patients with a median age of 78 (range 49–89) years; 40 (75 per cent) were men, 26 (49 per cent) were diabetic, 24 (45 per cent) were hypertensive, 19 (36 per cent) had symptomatic coronary artery disease and ten (19 per cent) had symptomatic cerebrovascular disease.

Twenty (36 per cent) of the 55 limbs treated by PTA alone caused rest pain, 16 (29 per cent) had ulceration and 19 (35 per cent) had gangrene. The median ankle:brachial pressure index (ABPI) was 0·43 (range 0·22–0·85). The primary reason for choosing PTA was high anaesthetic risk in 29 cases (53 per cent) and eminent suitability for PTA in 26 (47 per cent). Forty-two procedures (76 per cent) were to a single arterial segment, 12 (22 per cent) to two segments and one (2 per cent) to three segments; 45 procedures (65 per cent) were for stenosis and 24 (35 per cent) for occlusion. The most distal PTA was at or below the popliteal artery in 16 of 55 procedures (29 per cent). There were three complications, all minor emboli that were successfully aspirated percutaneously. There were no deaths or tissue loss directly attributable to PTA.

Five PTAs (9 per cent) were technical failures and a total of seven procedures (13 per cent) failed to produce a symptomatic improvement. The median increase in ABPI was 0·25 (range 0·00–0·65), with 87 per cent of patients experiencing an immediate symptomatic improvement that was maintained in 85 per cent at 3 months. Some 80 per cent of limbs with ulceration or gangrene had healed with minor surgery by a median of 7·5 (range 3–18) months. The 36-month haemodynamic and symptomatic actuarial patency rates were 78 and 77 per cent. The actuarial patency rate at 36 months was significantly less for procedures at or below the popliteal artery (71 per cent) than for those above (94 per cent) ($P = 0{\cdot}034$, log rank test). The actuarial limb salvage rate at 36 months was 89 per cent and patient survival 76 per cent.

It is concluded that PTA has a crucial role to play in the management of the critically ischaemic limb. Of limbs treated by PTA alone (24 per cent of the total), the majority (87 per cent) improved immediately, with a 3-year actuarial haemodynamic patency rate, including technical failures, of 78 per cent and a limb salvage rate at 3 years of 89 per cent.

Subintimal angioplasty of femoropopliteal artery occlusion: long-term results

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From January 1987 to April 1992 the technique of subintimal percutaneous transluminal angioplasty (PTA) was attempted on 200 consecutive femoropopliteal artery occlusions. The median length of occlusion was 11 (range 2–37) cm; 178 procedures (89 per cent) were performed for claudication and 22 (11 per cent) for critical ischaemia. The principle of the technique is deliberately to enter the subintimal plane immediately proximal to the occlusion, traverse the occlusion in the subintimal plane, and exit immediately distal to the occlusion. Recanalization is then achieved by inflating the angioplasty balloon within the subintimal space.

The initial technical success rate was 159 of 200 procedures (80 per cent) and was not significantly different for occlusions $\leqslant 10$ cm (81 per cent, $n = 73$), 11–20 cm (83 per cent, $n = 63$) or >20 cm (68 per cent, $n = 23$) in length ($P = 0{\cdot}20$). There were two serious complications (1 per cent): one retroperitoneal and one scrotal haematoma, both requiring surgical evacuation. There were no deaths or limb losses resulting from the procedure.

The median (range) ankle:brachial pressure index increased from 0·61 (0·21–1·0) before to 0·90 (0·26–1·50) after PTA. The actuarial haemodynamic patency rates at 12 and 48 months were 71 and 41 per cent respectively; the symptomatic patency rates were 73 and 51 per cent. Multiple regression analysis using the Cox proportional hazards method (variables of sex, diabetes, claudication/critical ischaemia, hypertension, smoking, aspirin use, calf vessel run-off, femoral artery diameter, occlusion length) showed that smoking carried a risk multiplier of 2·70 ($P < 0{\cdot}001$), each additional run-off vessel reduced the relative risk by 0·54 ($P < 0{\cdot}001$) and the risk increased by 1·73 ($P = 0{\cdot}02$) for every 10 cm of occlusion. No other variable was significant.

In conclusion, the technical success rate of subintimal angioplasty for femoropopliteal occlusion is unrelated to the length of the lesion because the occlusion is traversed in an extraluminal plane. Excellent cumulative symptomatic and haemodynamic patency rates can be achieved at 4 years (51 and 41 per cent respectively) with a low complication rate. The factors influencing patency at 4 years were smoking, the number of calf run-off vessels and length of occlusion.

Femoropopliteal angioplasty for severe limb ischaemia

I.C. Currie, C. Wakeley, S.E.A. Cole, M.G. Wyatt, R.N. Baird and M. Horrocks, *Bristol Royal Infirmary, Bristol, UK*

Percutaneous transluminal angioplasty (PTA) is established in the treatment of short isolated lesions in claudicants but its role in critical ischaemia is controversial.

Between July 1983 and July 1987, 50 patients underwent 51 PTA procedures to the femoropopliteal segment for critical ischaemia. Twenty had distal gangrene, 13 persistent foot ulcers, and 17 rest pain with ankle pressure <60 mmHg. Criteria for success were a rise of 0·1 in the ankle:brachial pressure index and symptomatic improvement. Patients were seen and regularly assessed in a vascular studies unit. Angiograms were independently reviewed and scored by vascular radiologists.

There were eight complications: seven occurred during attempts to dilate long (>5 cm) occlusions. Five of these patients subsequently underwent amputation. Secondary procedures after PTA are shown below.

	Failed attempt ($n = 11$)	Failed after <6 months ($n = 25$)	Successful after $\geqslant 6$ months ($n = 14$)
Amputation	8	8	1
Bypass surgery	2	4	0
PTA or streptokinase	1	5	0

Primary and secondary limb salvage rates at 2 years were 51 and 66 per cent respectively. Patients with long lesions and poor run-off had a high failure rate. Of 23 long occlusions dilated, 22 failed. Of 14 patients with successful results at 6 months, 13 had short lesions dilated.

Overall, angioplasty had a low chance of long-term success; however, selected patients obtained limb salvage from a minimally invasive procedure. On the basis of this series, angioplasty of long lesions is associated with high complication and failure rates and PTA should be reserved for patients with short occlusions.

Haemodynamic changes following percutaneous transluminal angioplasty of the lower limb

S.A. Ray, T.M. Buckenham, R.S. Taylor and J.D. Dormandy, *St George's Hospital, London, UK*

The haemodynamic changes following percutaneous transluminal angioplasty (PTA) of the lower limb have not been extensively studied, especially during the first 24 h. Recent work has suggested an inexplicable delay of up to 1 month in reaching the final ankle:brachial pressure index after successful PTA. Although antispasmodic drugs are often given empirically after PTA, there is no evidence supporting their use or studies of their effects on haemodynamic changes.

A total of 24 patients undergoing technically successful PTA of the lower limb were randomized to receive a single intra-arterial bolus of either 150 μg glyceryl trinitrate or saline immediately after completion of the procedure. Toe:brachial pressure indices and laser Doppler fluxmetry were closely monitored in the first 24 h and measurements repeated after 1 week and 1 month.

The group given saline ($n = 11$) showed no significant haemodynamic improvement for 6 h following PTA, after which the toe:brachial index increased slowly over 1 month. The group given glyceryl trinitrate ($n = 13$) showed an immediate peak that subsided over 6 h before indices increased again slowly. The toe:brachial index attained at 1 month was similar to that reached immediately after administration of glyceryl trinitrate and was twice that reached in the group given saline.

It has been shown, therefore, that there is a 6-h delay in the toe:brachial index rise following successful PTA and that the increase at 1 month is twice as great in patients given glyceryl trinitrate immediately after the procedure. There was a similar pattern in the laser Doppler flux results.

Skeletal muscle reperfusion injury: role of the neutrophil and endothelium

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Alterations in neutrophil and endothelial cell function promote skeletal muscle reperfusion injury, although their relative importance is unclear. Therefore in a rat model of 6-h unilateral hindlimb ischaemia and 4-h reperfusion, gastrocnemius muscle viability (nitroblue tetrazolium assay) and oedema (wet:dry weight) were assessed (experimental: contralateral normal limb) in ten normal rats (no ischaemia), ten controls (6-h ischaemia and 4-h reperfusion) and ten ischaemic animals (6-h ischaemia alone). Results were compared with those in 12 rats rendered neutropenic by antineutrophil serum (ANS) and in 12 receiving the leukotriene B_4 (neutrophil chemotaxis, activation) receptor antagonist (LTB_4 RA) SC41930 at 1 mg per kg per 4·5 h by intravenous infusion commencing 30 min before reperfusion.

ANS reduced the median (range) neutrophil count before ischaemia from 825 (560–1355) mm^{-3} in controls to 55 (40–145) mm^{-3} ($P < 0{\cdot}001$).

Group	Viability index	Oedema index
Normal	1·00 (1·00–1·00)	1·00 (0·98–1·01)
Ischaemia	1·00 (1·00–1·00)	1·01 (0·99–1·03)
Control	0·53 (0·33–0·61)	1·61 (1·28–1·69)
ANS	1·00 (1·00–1·00)	1·64 (1·37–1·73)
LTB_4 RA	1·00 (1·00–1·00)	1·08 (1·05–1·10)

Values are median (interquartile range)

The 6-h ischaemia caused neither muscle infarction nor oedema (P not significant *versus* normal), while reperfusion resulted in both ($P < 0{\cdot}01$, control *versus* normal and ischaemia). These changes were prevented by the LTB_4 RA (P not significant *versus* normal and ischaemia; $P < 0{\cdot}01$ *versus* control) but only muscle viability was preserved in neutropenic animals ($P < 0{\cdot}01$ *versus* control; P not significant *versus* normal and LTB_4 RA) with oedema still developing (P not significant *versus* control; $P < 0{\cdot}01$ *versus* normal, ischaemia and LTB_4 RA). While the results confirm the role of neutrophils in the pathogenesis of postischaemic muscle necrosis, it appears that endothelial lipid peroxidation, an alternative source of LTB_4 in neutropenic animals, promotes the microcirculatory failure that characterizes reperfusion injury.

Success and failure in graft surveillance: prospective trial results

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Quickscan (QS) is a disease-mapping technique using continuous-wave Doppler ultrasonography. This is offered as a superior alternative to ankle:brachial pressure index, impedance, colour duplex and digital subtraction angiography (DSA) in active maintenance of graft patency. Stenosis magnitude is expressed as an area ratio and can range between 1:3 and 1:6 (equivalent to 42 per cent to over 75 per cent). Correlations using DSA as the 'gold standard' gave a sensitivity of 84 per cent and specificity of 91 per cent in detection of significant stenosis. The fate of 55 infrainguinal grafts has been followed using QS at a nominal interval of 6 weeks and DSA every 12 weeks.

Graft material was polytetrafluoroethylene (29 grafts), reversed vein (14), *in situ* vein (nine) and hybrid constructions (three). There were five early failures, leaving 50 grafts for surveillance.

Graft status	No.*	Stenosis†	Graft life (months)†
Still patent	27 (54)	None	8 (1–13)
Stenosis			
No intervention	13 (26)	1:3 (1:3 to 1:4)	11 (3–12)
Successful PTA	1 (2)	1:6	11 patent
Unsuccessful PTA	1 (2)	1:4	8 occluded
Then occlusion	8 (16)	1:6 (1:3 to 1:6)	5 (1–8) occluded

*Values in parentheses are percentages; †values in parentheses are ranges. PTA, percutaneous transluminal angioplasty

Of the eight patients with occlusion, PTA was not attempted in two due to equivocal stenosis on DSA, one stenosis was inaccessible and five occluded without intervention.

It is concluded that: 46 per cent of grafts developed significant stenoses $\geqslant 1{:}3$; 20 per cent of grafts occluded after developing stenoses averaging 1:6; PTA should be applied rapidly once stenoses $\geqslant 1{:}4$ develop; and QS accuracy suggests that DSA could be reserved for intervention. The demand on scanning time imposed by the graft surveillance protocol has encouraged development of a new system. This portable unit is designed to achieve a 10-min graft assessment, supplying an unequivocal anatomical map of the disease process.

Natural history of the angioplastied artery

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Percutaneous transluminal angioplasty of superficial femoral artery lesions now has an accepted role in vascular surgical practice. The long-term effect of the vessel wall trauma caused by the balloon is not yet fully understood and hence the present study was undertaken.

A total of 51 patients with 105 lesions (76 stenoses, 29 occlusions) were examined with detailed colour-flow duplex scanning before and 1 day after balloon angioplasty. There were six immediate reocclusions; the remaining 45 patients were followed for at least 6 months or until further intervention.

Duplex scanning showed that 39 patients had developed significant stenosis again. There have been 19 patients with 21 persistent high-velocity lesions seen immediately after the procedure. Of these, 15 improved but 11 were to become recurrent; nine showed plaque fracture dissection or thrombus at the time. Of the other six stenoses, three patients died and three stenoses persisted; only one showed dissection. There were also 14 patients with 21 recurrent lesions seen on duplex scan; 11 had plaque fractures, dissection or thrombus. Eighteen patients developed 20 new stenoses. Of these 39 patients, 20 are symptomatic but only four are the same or worse than before. For these patients duplex evidence of haemodynamically significant stenosis occurred at a mean of 5·9 weeks but symptomatic onset was at a mean of 13·7 weeks.

Duplex scanning detects a high incidence of recurrent stenoses after angioplasty (76 per cent); however, the rate of symptomatic recurrence is much less (39 per cent). Immediate postdilatation scanning reveals a particular group at high risk of recurrence, i.e. those with persistent high velocity in the presence of plaque fracture, dissection or thrombus.

Announcement

Frank Glenn Travelling Fellowship 1993

The International Hepato-Biliary-Pancreatic Association invites applications for the above travelling Fellowship. A stipend of 500 SFr is available to subsidize a young investigator in the field of hepatobiliary and pancreatic disorders. The applicant must be sponsored by a member of the Association. The stipend may be used to support a laboratory project and/or to subsidize travel expenses that are deemed appropriate to the field of investigation. Applicants must be under 40 years of age and should have an established record of at least one or several papers concerning liver, biliary or pancreatic disease.

Applications should be made in writing and should include the following:
1. A copy of the applicant's *curriculum vitae.*
2. A summary of 1–2 pages of a research protocol describing how the stipend is to be used.
3. A letter of nomination from a member of the IHBPA or the applicant's Department Chair.

Applications should be sent to: Professor A. Cuschieri, University Department of Surgery, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK. Telephone: (0382) 60111 Extn 2174; Fax: (0382) 641795.

A. Cuschieri

SURGERY ABSTRACTS

Br. J. Surg. 1993, Vol. 80, April, 533–534

A selection from the March issue of the American journal.

Aortic revascularization of orthotopic liver allografts: Indications and long-term follow-up

Hani A. Hennein, MD, Eric N. Mendeloff, MD, Jeremiah G. Turcotte, MD, John M. Ham, MD, Prabhakar Baliga, MD, Darrell A. Campbell, Jr., MD, *and* **Robert M. Merion, MD,** *Ann Arbor, Mich.*

Background. *Occasionally because of certain conditions that would imperil arterial supply to a hepatic graft, it is necessary to base the arterial supply on the aorta.*
Methods. *Twenty orthotopic liver transplants (OLTs) in 19 patients were performed with arterial revascularization based on the aorta (Ao-OLT). In two patients the donor celiac axis was anastomosed directly to the aorta and in 18 to a conduit anastomosed to either the supraceliac ($n = 10$) or infrarenal ($n = 8$) aorta.*
Results. *One thrombosis occurred 2 months after the placement of a supraceliac conduit in an adult patient, accounting for a cumulative 1-year hepatic artery patency rate of 91.7% ± 8.0% for 16 grafts placed in 15 adults and 100% for four grafts placed in four children. In comparison, hepatic artery–based transplantation was associated with a 1-year patency rate of 92.6% ± 1.9% for 245 adults and 94.7% ± 5.1% for 19 children (difference not significant compared with Ao-OLT). By logistic regression analysis, the only factor independently associated with hepatic artery thrombosis was retransplantation (1-year hepatic artery patency rate 85.7% ± 5.9% [$n = 38$] for retransplants vs 93.9% ± 1.7% for primary transplantation [$n = 246$]; $p < 0.05$). For retransplantation, Ao-OLT revascularizations were superior to those based on the hepatic artery (1-year patency rate 100% [$n = 11$] vs 79.9% ± 8.1% [$n = 27$]; $p < 0.05$).*
Conclusions. *Indications for Ao-OLT include poor hepatic arterial inflow, small or anomalous recipient hepatic arteries, friable or attenuated native hepatic arteries as may be present during retransplantation, and recipient age less than 1 year, especially those less than 15 kg or in whom the recipient artery is less than 3 mm in diameter. In these more precarious situations, Ao-OLT achieves patency rates similar to those of primary, uncomplicated OLT, is superior for retransplantation, and has technical advantages in the small pediatric liver recipient.* (SURGERY *1993;113:279-85.)*

Multiple primary melanoma: Incidence and risk factors in 283 patients

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To identify patients with melanoma at risk for a second primary lesion and to assess the prognostic relevance of multiple primary lesions, 7816 patients treated for malignant melanoma have been reviewed. Two to nine primary lesions were identified in 283 patients (3.6%): two lesions were identified in 82% of these 283 patients, three lesions in 11%, and four lesions in 3%. Sixty-four percent were metachronous. Among patients with melanoma, the 10-year actuarial risk of a second primary lesion was 5%; a third of that risk was expressed within 3 months of the initial diagnosis plus a subsequent risk of 0.38% per year. Risk factors for multiple primary lesions were family history of melanoma, thin primaries, male sex, Celtic complexion, and a history of another cancer. Patients with a family history of melanoma had a 14% risk of a second primary lesion during the first 10 years after diagnosis. By univariate and multivariate analyses, there was no survival disadvantage for patients with multiple primary lesions. After median follow-ups of 3.7 and 4.8 years, respectively, 51.7% and 50.5% of the groups with single and multiple primaries were disease free. Mortality rates were 31% and 25%, respectively. It is appropriate to base therapeutic decisions and prognostic evaluations on the specific risk factors of each individual lesion. Identification of patients at high risk for multiple primary lesions may permit early diagnosis and improved outcomes. (SURGERY *1993;113:330-9.)*

Lavage with leukotriene B_4 induces lung generation of tumor necrosis factor-α that in turn mediates neutrophil diapedesis

Gideon Goldman, MD, Richard Welbourn, MB, FRCSE, Lester Kobzik, MD, C. Robert Valeri, MD, David Shepro, PhD, *and* **Herbert B. Hechtman, MD,** *Boston, Mass.*

In experimental models of acute respiratory failure, leukotriene (LT) B_4 is generated in the lungs, followed by a 2- to 3-hour delay before there is substantial neutrophil (PMN) accumulation and increased permeability. This study tests whether lavage with LTB_4 induces tumor necrosis factor (TNF) synthesis by the lungs that in turn mediates PMN diapedesis. Anesthetized rats underwent lavage with 0.1 ml LTB_4 (10^{-6} mol/L) into a lung segment. This led to localized TNF synthesis measured in bronchoalveolar lavage fluid with peak concentrations of 580 pg/ml after $1\frac{1}{2}$ hours and 120 pg/ml after 3 hours. These values were higher than after lavage with 0.1 ml saline solution: 0.7 and 4.3 pg/ml, respectively (both $p < 0.05$). There was a delay before PMN accumulated in bronchoalveolar lavage fluid ($\times 10^4$). After 30 minutes, the numbers were 2.2 PMN/ml, whereas at 4 hours there was a rise to 40 PMN/ml and at 5 hours 60 PMN/ml, higher than after saline lavage (all $p < 0.05$). Pretreatment of rats by lavage into airways with actinomycin D, 12 ng in 0.1 ml, minimized LTB_4-induced TNF synthesis after $1\frac{1}{2}$ and 3 hours (38 and 51 pg/ml), as well as the delayed diapedesis after 4 hours (12 PMN/ml) (all $p < 0.05$). Similarly, pretreatment of other rats by lavage with TNF-α antiserum (rabbit anti-

murine), but not normal serum, limited LTB_4-induced diapedesis (13 PMN/ml) ($p < 0.05$). Interestingly, administration of the protein synthesis inhibitor actinomycin D by lavage 10 minutes after LTB_4 did not prevent TNF generation after $1\frac{1}{2}$ or 3 hours (490 and 440 pg/ml). However, this agent did limit PMN diapedesis after 4 hours (14 PMN/ml) ($p < 0.05$), an event possibly caused by limiting later synthesis of endothelial adhesion proteins, a thesis consistent with the findings that pretreatment of rats by lavage with actinomycin D was without any effect on N-formyl-methionyl-phenylalanine (10^{-8} mol/L)–induced diapedesis. This agent is known to induce PMN migration without need for synthesis of endothelial adhesion proteins. The data indicate that lavage with LTB_4 induces local TNF-α generation that in turn mediates a delayed PMN diapedesis. This event is likely regulated by endothelial synthesis of adhesion proteins. (Surgery 1993; 113:297-303.)

Use of a novel bioartificial liver in a patient with acute liver insufficiency

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We have developed a bioartificial liver support system (BAL) using porcine hepatocytes attached to microcarriers and placed on the outer surface of hollow fibers. The BAL system was attached to a plasmapheresis device that was then used to treat the plasma of a patient with acute liver failure. Our aim was to test the efficacy and safety of this system after a single short treatment period. A patient with alcohol-induced, severe, acute liver failure manifested by coagulopathy, rising plasma ammonia level, and deteriorating mental status was studied. The procedure was well tolerated by the patient, who remained hemodynamically stable throughout the treatment period. A marked increase in coagulation factor V, VII, VIII, and IX activities, a decrease in serum ammonia level (120 to 32 µmol/L), a twofold increase in all serum amino acids except for aminobutyric acid, and an improvement in mental status were noted after a 6-hour treatment period. This preliminary report of the first use of this novel BAL system in conjunction with plasmapheresis appears promising. A clinical study is now in progress to prove its efficacy. (Surgery 1993; 113:340-3.)

Prospective randomized study of routine intraoperative cholangiography during open cholecystectomy: Long-term follow-up and multivariate analysis of predictors of choledocholithiasis

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A prospective randomized study was performed to assess the value of routine intraoperative cholangiography (IOC) during cholecystectomy for gallstone disease. Four hundred and fifty-seven consecutive patients were screened for the presence of 11 predefined clinical criteria assumed to indicate choledocholithiasis. Two hundred and eighty patients who had no positive criteria and in whom preoperative endoscopic retrograde cholangiography had not been performed were randomized at the operating table to the IOC or no-IOC group. Follow-up was performed 6 to 8 years after the operation with a questionnaire and by use of clinical, biochemical, and radiologic investigations as indicated. Multivariate analysis was used to identify independent predictors of choledocholithiasis and the combination of criteria having the best predictive ability. The frequency of common bile duct calculi at operation was significantly correlated with age and with all clinical criteria except recent or present pancreatitis. However, only serum bilirubin level, cystic duct diameter, demonstration of common bile duct calculi on preoperative imaging or intraoperative palpation, and age at operation were independent predictors of choledocholithiasis. The overall best subset of clinical indicators contained all criteria with the exception of pancreatitis and alkaline phosphatase level. Negative predictive ability of the set of criteria was 100% for patients up to 60 years of age and 97% for patients older than 60 years at the time of operation. No case of residual common bile duct calculi was present in the IOC and no-IOC groups at follow-up. Our data strongly support a policy of performing IOC during cholecystectomy only when clinical criteria suggest the presence of common bile duct abnormalities or to clarify ductal anatomy. (Surgery 1993;113:318-23.)

Nonvascular emergencies presenting as ruptured abdominal aortic aneurysms

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Background. *Patients may present with signs and symptoms of ruptured abdominal aortic aneurysm (RAA) but actually have other diseases mimicking RAA. The outcome of these patients has not been reported.*

Methods. *During the past 10 years, 16 patients presumed to have RAAs were found at operation to have other diseases accounting for the symptoms. Fifteen patients (94%) had abdominal pain, 9 (56%) had a pulsatile abdominal mass, and 7 (44%) were hypotensive on presentation.*

Results. *Ten of the 16 patients had intact aortic aneurysms at surgery; there were no reliable physical signs or diagnostic tests that could discern between RAAs and intact aneurysms with other intraabdominal diseases. Eight patients (50%) died in the perioperative period, including four with widespread metastases, three with overwhelming sepsis, and one with an acute myocardial infarction. None of the 10 patients with aneurysms suffered RAA after emergency laparotomy. Exploratory laparotomy was necessary to treat underlying disease in nine patients and was probably harmful only to the patient with a myocardial infarction. Two survivors with aneurysms underwent successful staged repairs.*

Conclusions. *Mistaken diagnoses in patients who are suspected of having RAAs on the basis of physical findings are relatively uncommon. Exploratory laparotomies are required to correct the primary disease in most of these misdiagnosed patients. Few die as a direct result of laparotomy; true iatrogenic catastrophes associated with mistaken diagnoses are distinctly uncommon. (Surgery 1993;113:286-9.)*

Correspondence

Laparoscopic repair of perforated peptic ulcer

Sir

We read with interest the Surgical Workshop by Mr Sunderland and colleagues on laparoscopic repair of perforated peptic ulcer (*Br J Surg* 1992; **79**: 785). Our team performed six such repairs between March and October 1992. All patients were men, with a mean age of 35 (range 20–60) years. The duration from perforation to laparoscopy ranged from 8 to 12 h. Patients were selected according to accepted criteria for simple repair in perforated ulcers[1]. The size of perforation ranged from 3 to 6 mm. Peritoneal soiling was assessed as moderate in all cases. The perforation was repaired first by intracorporeal suture of the hole closed using 2/0 catgut tied in a surgeon's knot. Thereafter, a piece of omentum was placed over the site and attached to the sutures by tying or with Endo-Clips (Ethicon, Somerville, New Jersey, USA). In the first four cases four ports were needed (two of 11 mm, two of 5 mm) to complete the procedure. In subsequent cases, only three ports were used (two of 11 mm, one of 5 mm), as the omentum was held in place by putting the patient in the Trendelenburg position. The abdomen was washed thoroughly with 4–6 litres saline. The mean operating time was 80 (range 65–90) min. There were no postoperative complications. Bowel sounds commenced on the first or second day after operation and all patients resumed diet by the fourth. The average hospital stay was 5 (range 4–7) days. Follow-up ranged from 2 to 8 months. To date all patients have been asymptomatic except for one who complained of dyspepsia 2 months after operation; endoscopy did not reveal a recurrent ulcer.

The early experience of laparoscopic repair of perforated peptic ulcer is encouraging. The greatest benefit of laparoscopic repair will be seen in elderly patients, in whom problems of diagnosis coexist with appreciable morbidity and mortality[2]. More data are needed to evaluate this new approach. Furthermore, some patients will need definitive operation for ulcer diathesis[1]. Although the early results of laparoscopic vagotomy have been good[3], laparoscopic repair of a perforated ulcer combined with laparoscopic vagotomy in an emergency setting has not yet been performed. We are presently planning a controlled trial, which would complement our minimally invasive approach to peptic ulcer disease (*Table 1*).

Table 1 *Minimally invasive approach to peptic ulcer disease*[3,4]

Condition	Treatment
Intractable duodenal ulcer	Laparoscopic posterior truncal vagotomy and anterior seromyotomy
Benign intractable gastric ulcer	Laparoscopic Billroth II gastrectomy
Bleeding peptic ulcer	Endoscopic haemostasis to stabilize followed by laparoscopic surgery if indicated
Perforated peptic ulcer	Laparoscopic simple repair or definitive surgery as indicated
Pyloric stenosis	Laparoscopic truncal vagotomy and gastrojejunostomy

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1. Hugh TB. Perforated peptic ulcers. In: Schwartz SI, Ellis H, eds. *Maingot's Abdominal Operations.* Norwalk, Connecticut: Appleton and Lange, 1990: 627–47.
2. Irvin TT. Mortality and perforated peptic ulcer: a case for risk stratification in elderly patients. *Br J Surg* 1989; **76**: 215–18.
3. Kum CK, Goh PMY. Laparoscopic vagotomy: a new tool in the management of peptic ulcer disease. *Br J Surg* 1992; **79**: 977 (Letter).
4. Goh PMY, Tekant Y, Kum CK, Isaac J, Ngoi SS. Totally intra-abdominal laparoscopic Billroth II gastrectomy. *Surg Endosc* 1992; **6**: 160.

Laparoscopic abdominoperineal resection of the rectum

Sir

Dr Sackier and colleagues recently reported (*Br J Surg* 1992; **79**: 1207–8) a case of laparoscopic abdominoperineal resection of the rectum for a benign condition and highlighted the concern about obtaining an adequate margin of resection if malignant lesions are subjected to a laparoscopic approach. We present a case of a primary adenocarcinoma located at the anal margin that was successfully treated by abdominoperineal resection assisted by laparoscopy.

A 48-year-old woman presented with a 4-cm nodule located in the perineal area between the vaginal fornix and the right anterior quadrant of the anus. The lesion was not ulcerated and there was no inguinal adenopathy. Biopsy demonstrated an adenocarcinoma. Colonoscopy, liver ultrasonography and computed tomography ruled out associated lesions. Endorectal ultrasonography revealed invasion of the external anal sphincter, and abdominoperineal resection of the rectum was proposed.

Pneumoperitoneum was created, and the abdominal cavity explored by laparoscopy. Five ports were used: two of 5 mm, two of 12 mm and one of 10 mm. The sigmoid colon was mobilized, and the inferior mesenteric vessels were ligated after visualization of the ureters. The peritoneal reflection was opened, and the rectum was dissected, including the posterior mesorectum. When the abdominal procedure was finished, the perineal dissection was started with a fusiform incision that included the perineal body with an adequate margin of skin and subcutaneous fat, the posterior wall of the vagina and the anus. The whole specimen was excised through the perineum. The perineal defect was closed with several layers of absorbable sutures, and an end colostomy was constructed through the trocar hole in the left iliac fossa. Postoperative recovery was satisfactory, with oral feeding at 48 h and discharge from hospital 7 days after operation.

After the rapid spread of laparoscopic cholecystectomy, many types of abdominal procedure have been attempted by this approach. Although colonic resection is feasible by laparoscopy[1–4] and some large series suggest a satisfactory oncological resection of colonic carcinoma[3], there is no general agreement about the long-term safety of colorectal resection assisted by laparoscopy. Comparative studies are lacking[4]. In the case presented, in which the radical operation was performed by a perineal approach, laparoscopy for the abdominal dissection did not preclude satisfactory oncological treatment of the tumour. We suggest that laparoscopy may play an important role in the treatment of selected malignant tumours located in the anus or perineal region.

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1. Schlinkert RT. Laparoscopic assisted right hemicolectomy. *Dis Colon Rectum* 1991; **34**: 1030–1.
2. Saclarides TJ, Ko ST, Airan M, Dillon C, Franklin J. Laparoscopic removal of a large colonic lipoma. *Dis Colon Rectum* 1991; **34**: 1027–9.
3. Monson JR, Darzi A, Carey PD, Guillou PJ. Prospective evaluation of laparoscopic assisted colectomy in an unselected group of patients. *Lancet* 1992; **340**: 831–3.
4. McFayden BV, Wolfe BM, McKernan JB. Laparoscopic management of the acute abdomen, appendix, and small and large bowel. *Surg Clin North Am* 1992; **72**: 1169–83.

Perforation of the bowel by suction drains

Sir
The cautionary letter from Mr Oppong and colleagues (*Br J Surg* 1992; **79**: 1384) about injuries from suction drains is well taken. Ordinary suction drains draw omentum into suction holes, making their removal often a bloody and painful experience for the patient. Blake drains (Johnson and Johnson, New Brunswick, New Jersey, USA) eliminate these risks. Over nearly a decade these drains have worked effectively and their removal is painless. The key element in these drains is the channelled configuration.

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The Case Report by Mr Reed and colleagues (*Br J Surg* 1992; **79**: 679) elicited a good deal of interest, but the subject is now closed.
Editor

Prospective randomized trial comparing the Shouldice technique and plication darn for inguinal hernia

Letter 1

Sir
I read with interest the paper by Mr Kingsnorth and colleagues (*Br J Surg* 1992; **79**: 1068–70). The presentation of the results and the conclusions drawn from the study deserve closer examination. The underlying supposition of the paper is that the Shouldice repair, even when undertaken in non-specialist centres, has a significantly lower recurrence rate than plication darn – otherwise why use it? The authors suggest that an extended period of supervision is required to reduce the number of technical failures.

Although the paper states that the trial had not shown the superiority of the Shouldice repair, the authors indicate that, given adequately trained staff, it would. The data presented fail to support this conclusion. First, the consultant surgeon had one recurrence (Shouldice?) in the first 2 years; if indeed this was a recurrence in the Shouldice group, it equates to a 2-yearly recurrence rate of 4 per cent (one of 25). In comparison, the junior surgeons had a recurrence rate in the Shouldice group of 4·8 per cent (six of 126). These figures hardly imply that great benefit will be gained by further supervision and experience. Second, if one compares the plication darn method with the Shouldice technique, the junior staff at 2 years had a 2·7 per cent recurrence rate (four of 148) and the consultant a rate of zero (none of 23). Both of these results were a considerable improvement on the equivalent groups undertaking the Shouldice repair.

The important point from this paper is whether the UK should move to the development of specialist hernia centres as in Canada to reproduce their impressive recurrence figures rather than persist with a possibly second-rate service provided by non-specialist centres.

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Authors' reply

Sir
We thank Mr Carter for his observations, which are apparent but not statistically significant. Retrospectively it is possible to compare many subsets of patients in any clinical study, but the only valid statistical comparisons should be made between groups that were predetermined before the study was initiated. It was an error in the manuscript not to state in which group the consultant's recurrence occurred; it was actually after plication darn. In support of our conclusion, a recent study by Panos and colleagues[1] has shown that, in the hands of resident surgeons in general surgery at an airforce hospital in Texas, USA, the recurrence rate for the Shouldice repair at a mean follow-up of 36·4 months is 6·6 per cent.

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1. Panos RG, Beck DE, Maresh JE, Harford FJ. Preliminary results of a prospective randomized study of Cooper's ligament *vs* Shouldice herniorrhaphy technique. *Surg Gynecol Obstet* 1992; **175**: 315–19.

Letter 2

Sir
We congratulate Mr Kingsnorth and colleagues on their important study comparing plication of the posterior wall of the inguinal canal with the Shouldice repair (*Br J Surg* 1992; **79**: 1068–70). Although the recurrence rates are higher than those reported from series where surgeons with a special interest undertook Shouldice repairs, they probably are a true representation of what can be achieved in a standard surgical setting. While juniors are fully aware of the published advantages of Shouldice repair, the relatively small number of surgeons routinely performing this operation has often prevented them from being trained in the technique[1]. Mr Kingsnorth appears to have demonstrated what many believe: that the exact technique used is not important so long as careful attention is paid to the posterior wall of the inguinal canal.

We cannot accept the second conclusion that the high recurrence rate is attributable to inadequately trained junior surgeons. Although the senior author had only one recurrence, this was from a total of 48 operations (2 per cent). The remaining surgeons in the study had ten recurrences of 274 (3·6 per cent); this is not statistically significant. Furthermore, as there were a total of 14 junior surgeons, at least four of them had no recurrence whatsoever and therefore performed slightly better than their senior colleague.

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1. Morgan M, Swan AV, Reynolds A, Beech R, Devlin HB. Are current techniques of inguinal hernia repair optimal? A survey in the United Kingdom. *Ann R Coll Surg Engl* 1991; **73**: 341–5.

Authors' reply

Sir
We welcome the comments of Messrs Manson and Reed with respect to the first paragraph of their letter. Regarding their comments about the difference in recurrence rate between the consultant and his junior colleagues, we refer them to our observations in reply to a previous letter (*Br J Surg* 1993; **80**: 403). We are sure that the figures can be 'massaged' in many respects, but defy Messrs Manson and Reed to produce a *P* value from our data to demonstrate any difference in recurrence rate between the consultant and individual junior surgeons.

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Non-steroidal anti-inflammatory drugs and appendicitis in patients aged over 50 years

Sir

We read with interest the recent article by Messrs Campbell and De Beaux (*Br J Surg* 1992; **79**: 967–8), which suggested a relationship between non-steroidal anti-inflammatory drug (NSAID) use and appendicitis in patients aged 50 years or over. Although the odds ratio was estimated at 6·5, the 95 per cent confidence interval (c.i.) was large (2·1–8·8), presumably due to the effect of small numbers. However, no attempt was made to interpret this association with respect to its impact on the population of a typical health district. Assuming the association described is a causal one, the proportion of appendicitis associated with NSAID usage in a given population can be calculated as the attributable proportion (P_a) using standard formulae[1]:

$$P_a = \frac{p(\mathrm{RR} - 1)}{p(\mathrm{RR} - 1) + 1}$$

where RR is the relative risk (nearly the same as the odds ratio) and p the prevalence of exposure to the risk factor in the total population. The prevalence of NSAID use in the authors' control series was 11 per cent, similar to other estimates[2]. Thus the proportion of appendicitis in their source population attributable to NSAID usage can be calculated to be 37·7 per cent (95 per cent c.i. 10·8–46·2 per cent).

Among Nottingham Health Authority residents aged 50 years or over, in the 4 years from April 1987 to April 1991, 192 emergency or elective appendicectomies were performed as a primary surgical procedure; this figure excludes those performed opportunistically during the course of other procedures and gives a yearly mean of 48. If the authors' findings can be generalized, and in the unlikely circumstance that all appendices removed in Nottingham were genuinely inflamed then, as a direct result of NSAID usage, an estimated 18 cases of appendicitis (95 per cent c.i. 5·2–22·2) occurred in each of the past 4 years within a population of approximately 192 000 aged 50 years or over[3]. While fully accepting that appendicitis can pose serious problems in an elderly person, and notwithstanding the well documented detrimental effects of NSAIDs on the upper gastrointestinal tract, this additional effect still seems a small price to pay for the freedom from pain, mobility and independence that NSAIDs give to very many elderly people.

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1. Elwood JM. *Causal Relationships in Medicine: a Practical System for Critical Appraisal.* Oxford: Oxford University Press, 1988.
2. Langman MJS, Morgan L, Worral A. Use of anti-inflammatory drugs by patients admitted with small or large bowel perforation and haemorrhage. *BMJ* 1985; **290**: 347–9.
3. Office of Population Censuses and Surveys. *Population Projections: 1985–2001.* PP3 no. 7. London: HMSO, 1985.

Authors' reply

Sir

As Mr Baker and colleagues point out, the number of patients affected by the increased risk of appendicitis related to use of non-steroidal anti-inflammatory drugs (NSAIDs) is low compared with those experiencing upper gastrointestinal tract problems. In contrast to the upper intestinal tract, however, no strategies for protection of the large bowel yet exist in the face of continued exposure to NSAIDs. Although no high-risk group can be identified for appendicitis, these data together with those previously reported for diverticular complications[1] suggest that the entire large intestine is at increased risk of septic complications during NSAID ingestion. Thus patients with symptomatic diverticular disease, for instance, may well be advised to avoid such drugs. While NSAIDs remain indispensible symptom-relieving agents, they confer no survival benefit and do not reverse disease pathogenesis; indeed in osteoarthritis, their most common indication in our studies, they can accelerate joint destruction[2]. The existence of site-specific differences in individual NSAID activity[3] influencing their adverse effects profiles[4] is now appreciated. Perhaps a more critical attitude towards NSAID prescription is required rather than acceptance of the status quo.

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1. Campbell KL, Steele RJC. Non-steroidal anti-inflammatory drugs and complications of diverticular disease: a case–control study. *Br J Surg* 1991; **78**: 190–1.
2. Rashad S, Revell P, Hemingway A *et al.* Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *Lancet* 1989; **ii**: 519–22.
3. Vane JR, Botting RM. The mode of action of anti-inflammatory drugs. *Postgrad Med J* 1990; **66**(Suppl 4): 2–17.
4. Balfour JA, Buckley MT. Etodolac: a reappraisal of its pharmacology and therapeutic use in rheumatic diseases and pain states. *Drugs* 1991; **42**: 274–99.

Laparoscopic operations in paediatric surgery

Sir

I read with interest the recent Leading Article by Mr Miller (*Br J Surg* 1992; **79**: 986–7). With reference to the role of laparoscopy in the management of the impalpable testis, I have developed a new technique for single-stage mobilization and fixation of intra-abdominal or canalicular testes. After locating an intra-abdominal testis, mobilization of the spermatic vessels is carried out by incising the peritoneum of the posterior abdominal wall. The vas is also mobilized with a thin peritoneal pedicle carrying its blood supply. The gubernaculum is then divided, and the testis is now free at the end of its vessels and vas. A canalicular testis is dealt with by incision of the deep ring and tracing the cord into the inguinal canal to free the testis and replace it in the peritoneal cavity.

After creating a dartos pouch, an artery forceps is passed from the scrotum into the peritoneal cavity under laparoscopic control. This manoeuvre can be performed through the inguinal canal or medial to the inferior epigastric vessels if more length is desired. The forceps grasps the remnant of the gubernaculum or the tunica, and the testis is pulled down to be fixed in the scrotum.

Although the Fowler–Stephens manoeuvre remains an option, I feel it should not be performed on every intra-abdominal testis (as was advocated recently[1,2]). Smolko and colleagues[3] reported that 63 per cent of intra-abdominal testes were successfully placed into the scrotum by standard cord mobilization techniques.

This technique offers the surgeon therapeutic options including low orchidopexy through controlled maximum mobilization, transposition of cord exit point, Fowler–Stephens manoeuvre or a staged orchidopexy if necessary, as well as dealing with a hernia sac. It saves the patient inguinal or even abdominal incisions, and its advantages are doubled in cases of bilateral impalpable testis.

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1. Bloom DA. Two-step orchiopexy with pelviscopic clip ligation of the spermatic vessels. *J Urol* 1991; **145**: 1030–3.
2. Heiss KF, Shamdling B. Laparoscopy for the impalpable testis: experience with 53 testes. *J Pediatr Surg* 1992; **27**: 175–9.
3. Smolko MJ, Kaplan GW, Brock WA. Location and fate of the nonpalpable testis in children. *J Urol* 1983; **129**: 1204–6.

Laparoscopic herniorrhaphy

Sir

The question of laparoscopic hernia repair has arisen in our hospital; we have been offered some £7000 to undertake 24 of these operations. I have seen the technique demonstrated and believe that it is not technically difficult and could be performed by any district hospital surgeon.

However, I am much less convinced of the need for this technique, and am rather concerned about the prospects of complications in the learning stages for each surgeon. To be of value this operation must prove its superiority over conventional herniorrhaphy in one of three ways: decreased complication rate, decreased recurrence rate, or greater cost effectiveness.

In reverse order, laparoscopic herniorrhaphy is clearly not cost effective, because the apparatus required for the procedure does take up some extra money that is not required for conventional herniorrhaphy. Second, the recurrence rate for conventional herniorrhaphy in the best hands is about 0·3 per cent; it is difficult to imagine any other technique improving on this, but it is possible that the laparoscopic procedure could produce equally good results. This possibility has yet to be proved. Third, there are reports of horrifying complications such as stapling the femoral artery and, in one local case, a large scrotal haematoma that eventually required orchidectomy.

If more short-stay or daycase surgery was the policy, I cannot see how the laparoscopic approach can make any improvement in cost effectiveness. I believe, as did Mr Macintyre in a recent Leading Article (*Br J Surg* 1992; **79**: 1123–4), that this procedure should be restricted to a few centres and that no definite conclusion should be drawn until at least 300 operations have been performed in a double-blind controlled trial with a minimum follow-up of 3 years. Furthermore, I think it is unethical to submit patients to these operations without a full explanation of the possible risks, including that the surgeon is inexperienced and that complications and recurrence are much more likely in the early stages. If this explanation were given, I believe that the take-up rate would probably be less than 50 per cent; in any event I refuse to let my patients be the testbed for an experimental procedure.

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Laparoscopic cholangiography: a simple inexpensive technique using readily available materials

Sir

I read with interest the recent Surgical Workshop by Mr Harvey and colleagues (*Br J Surg* 1992; **79**: 1178–9) on laparoscopic cholangiography. The authors' 90 per cent success rate is comparable to that of another series using the same technique[1]. A similar method has been described previously[2], employing either a mushroom-tip or ureteric catheter introduced into the abdominal cavity through a 14-Fr Angiocath sheath (Becton–Dickinson, Oxford, UK). This author also recommended the use of radiolucent ports to eliminate the problem of overlying hardware obscuring the view.

The figure of approximately 20 000 laparoscopic cholecystectomies performed in the USA alone quoted by Harvey and colleagues refers to the total number performed to the end of 1990 only[3]. The rapid increase in the use of this procedure has continued. It was reported at the Society of Minimally Invasive Therapy meeting in Dublin, Ireland, in November 1992 that 125 000 laparoscopic cholecystectomies were performed in the USA in 1991 (25 per cent of all cholecystectomies) and that this figure would increase to 400 000 (80 per cent) in 1992.

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1. Fullarton GM, Bell G. The role of operative cholangiography in laparoscopic cholecystectomy. *Minimally Invasive Therapy* 1992; **1**(Suppl 1): 75.
2. Olsen DO. Laparoscopic cholecystectomy. *Am J Surg* 1991; **161**: 339–43.
3. Schirmer BD, Edge SB, Dix J, Hyser MJ, Hanks JB, Scott Jones R. Laparoscopic cholecystectomy. Treatment of choice for symptomatic cholelithiasis. *Ann Surg* 1991; **213**: 665–77.

Monitoring and cerebral protection during carotid endarterectomy

Sir

I read with interest the Review by Mr Naylor and colleagues on carotid endarterectomy (*Br J Surg* 1992; **79**: 735–41). The authors state that a technician and access to a neurophysiologist are necessary to perform both electroencephalography (EEG) and evoked potential monitoring during operation. In addition, they refer to the effects of different anaesthetic agents and haemodynamic variables on these recordings. I therefore suggest that, if these techniques are to prove beneficial and become routinely used, the presiding anaesthetist is the most suitable person to supervise and/or perform them. As an anaesthetist, I have had experience in this field and believe that this type of monitoring will be valuable only if the findings are accurately interpreted in the light of all the surgical and physiological events in the operating room. The constant presence of a skilled interpreter is thus paramount. This clearly becomes a practical impossibility for neurophysiologists as the expected demand for this type of operation increases.

The obvious criticism of my proposal concerns the increased workload for the anaesthetist. This increase can now be largely offset by the advent of improved user-friendly computer programs[1,2]. In agreement with previous authors, I believe that these systems allow easy handling and interpretation of EEG and evoked potential signals by physicians other than those trained specifically in neurology[3]. Finally, the savings arising from optimal use of operating room personnel are another important advantage in the current financial climate.

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1. John ER, Chabot RJ, Prichep LS, Ransohoff J, Epstein F, Berenstein A. Real-time intraoperative monitoring during neurosurgical and neuroradiological procedures. *J Clin Neurophysiol* 1989; **6**: 125–58.
2. Chabot RJ, John ER, Prichep LS, Landau RM, Isom WV, Gugino LD. Real-time multichannel quantitative EEG monitoring. In: Willner A, ed. *Cerebral Damage Before and After Cardiac Surgery*. Dordrecht: Kluwer, 1993.
3. Ross HH, Booij LHDH, de Lange JJ. The use of neurophysiological monitoring during anaesthesia. *Int J Clin Monit Comput* 1987; **4**: 179–84.

Presentation of abdominal tuberculosis to general surgeons

Sir

We read with interest the paper by Mr Underwood and colleagues (*Br J Surg* 1992; **79**: 1077–9) on the management of abdominal tuberculosis (TB). Diagnosis in a large proportion of patients was achieved by lymph node biopsy during laparotomy. We have recently treated two children with abdominal TB. The clinical features were suggestive of either gut lymphoma, abdominal TB or inflammatory bowel disease. The diagnosis of TB was achieved with ultrasound-guided fine-needle aspiration of peritoneal lymph nodes with the patient under sedation. Both children responded well to subsequent antituberculous chemotherapy. The use of percutaneous abdominal fine-needle biopsy under imaging guidance has proved to be an extremely useful diagnostic aid with a low complication rate[1,2]. Further, it has been shown to shorten hospital stay, decrease the need for more invasive procedures including anaesthesia and laparotomy and reduce considerably the cost of hospitalization[3].

A further six patients in the series of Underwood and colleagues received antituberculous chemotherapy without histological or microbiological evidence of disease. Abdominal TB may mimic many diseases; to embark on antituberculous chemotherapy without a firm diagnosis runs the risk of condemning the patient to a protracted unnecessary course of treatment or a delay in the true diagnosis[4]. A firm pathological diagnosis is thus essential and a bacteriological study to guide the appropriate chemotherapy is necessary. Once the diagnosis is confirmed and antituberculous chemotherapy is commenced early in the course of the disease, the prognosis is usually excellent.

1. Bret PM, Fond A, Casola G *et al.* Abdominal lesions: a prospective study of clinical efficacy of percutaneous fine-needle biopsy. *Radiology* 1986; **159**: 345–6.
2. Smith EH. Complications of percutaneous abdominal fine-needle biopsy. *Radiology* 1991; **178**: 253–8.
3. Rapaccini GL, Grattagliano A, Pompili M *et al.* Clinical suspicion of pancreatic neoplasm: does echo-guided fine-needle biopsy modify patient management? *Surg Endosc* 1990; 4: 206–8.
4. Wald A. Enteric tuberculosis: literature review. *Mt Sinai J Med* 1987; **54**: 443–9.

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Announcement

Surgery of the Liver, Biliary System and Pancreas

The British Council are holding a course devoted to Surgery of the Liver, Biliary System and Pancreas in The Royal College of Surgeons of Edinburgh from 17 to 23 October 1993. The course is intended for discussion of complex issues with an audience composed of relatively senior specialist surgeons. Topics to be covered will include: cholelithiasis and choledocholithiasis; minimally invasive hepatobiliary surgery; transplantation of liver and pancreas; acute and chronic pancreatitis; pancreatic and periampullary cancer; hepatobiliary trauma; portal hypertension; and hepatic and biliary malignancy. The course will be directed by Professor D. C. Carter, University Department of Surgery, The Royal Infirmary, Edinburgh.

Further information can be obtained from: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK.

D. C. Carter

Book reviews

Essentials of Paediatric Surgery. 4th ed.

H. Nixon and B. O'Donnell. 240 × 160 mm. Pp. 359. Illustrated. 1992. Oxford: Butterworth–Heinemann. £39·50.

The 4th edition of this well established general text on paediatric surgery appears after a gap of 14 years and is a fitting tribute to the late senior author, Mr Harold Nixon. It is based on the combined wisdom and vast experience of two eminent internationally renowned paediatric surgeons and authors. Considerable updating and revision has been necessary to keep pace with the medical and technical advances occurring in the 30 years since the first edition.

Each of the 46 chapters is essentially an essay in fluent narrative directed at a particular paediatric surgical problem. No attempt is made to adopt a systematic approach, and lists and tables are few. The style is pithy, witty and very readable. Potentially complex and contentious issues are reduced to clear and practical advice; the chapters on acute and recurrent abdominal pain are particular gems. Dogma is avoided, although some widely accepted practices, such as retraction of the foreskin for recurrent balanitis, are dismissed rather summarily. The coverage of the subject is comprehensive but, inevitably in a book of this handy size, occasionally brief (e.g. on child sexual abuse). Further elaboration of important concepts, such as the modified coma scale for head injury, would have been useful. The line drawings and clinical illustrations are carefully selected and clear, but some of the radiographic detail is lost in reproduction, such as those of necrotizing enterocolitis and oesophageal atresia. The references are brief but selected to include important historical and seminal papers.

This book should be read by beginners seeking a broad understanding of the specialty and re-read by practising surgeons wishing to gain insights into the attitudes of experts. As an updated classic it will continue to appeal widely.

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The Operative Management of Breast Disease

R. R. Baker and J. Niederhuber. 285 × 220 mm. Pp. 135. Illustrated. 1992. Philadelphia, Pennsylvania: W. B. Saunders. £83.

What is this book about and who are the intended readers? The first 14 pages deal with anatomy – all here may be seen in a standard anatomy text for premedical students. Breast infections are covered in a shallow fashion. The diagram of 'breaking down an abscess' might be useful in a book for nurses.

The operation of microdochectomy is well described but the management of nipple discharge given is muddled and discharge in postmenopausal women is said to be most usually from multiple ducts – not in my centre it isn't! A poor illustration of Paget's disease is produced. The entities of giant juvenile fibroadenoma (hamartoma) and of phyllodes tumour are confused. There are suggested managements in the book that are debatable, for instance the management of fibroadenoma by repeated examination (with mammography in young women) and excision of 80–90 per cent of the calcification for *diagnostic* biopsy in diffuse microcalcification.

From page 62 things get better. Indications for mastectomy and breast conservation are given and then good descriptions of operative technique for mastectomy, useful for the young surgeon in training; it is a pity that this lacks tips on avoiding the intercostobrachial nerve. The description of wide excision with breast conservation is inadequate and assumes that a previous open biopsy was required for diagnosis, which is now unusual in the UK. A good description of methods of breast reconstruction is given.

Readers may by now have the impression that I do not rate this book highly and they would be correct.

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Manual of Blood Transfusion in Clinical Medicine

S. Kareem (ed.). 215 × 138 mm. Pp. 212. Illustrated. 1992. New Delhi: All India Traveller Book Seller.

This book is written by the president and various officers of 'Lifeline', a blood transfusion service based in India. It covers such diverse aspects of blood transfusion as grouping, collecting, storing and administering blood, complications of transfusion, haemolytic disease of the newborn, bone marrow transplantation and blood substitutes. It would be of limited interest to UK surgeons, but might prove useful to those involved with blood transfusion services in the developing world. It contains a wealth of detail and as such is a proper handbook. Its advice relates to the resources available in India and many of the diseases found there, but no doubt much of this is applicable to other areas of the world. The chapters are written by different authors; the quality is variable and the language at times obscure but, in general, the book is straightforward and understandable.

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Cutaneous Facial Surgery

J. R. Thomas and J. Roller (eds). 284 × 220 mm. Pp. 207. Illustrated. 1992. Stuttgart: Georg Thieme. DM 178.

Over the past few years there have been a number of publications related to the subjects covered by this book. For the most part these have come from across the Atlantic and have been written by either dermatologists or otolaryngologists. No longer is the dermatologist confined to diagnosing rashes and prescribing ointments, nor the ear, nose and throat surgeon to his or her own stated surgical preserves. Both wish to embark on surgical procedures, some of which might be considered to be the province of the plastic and reconstructive surgeon, and indeed by a clever piece of nomenclature even call themselves 'facial plastic surgeons'. It is of interest that none of the main authors or 13 contributors in this book appears to be a plastic surgeon (as the term is generally understood in the UK) and virtually none of the copious references is from plastic surgery journals or books.

Setting these points aside, this book is an excellent reference for all who may be interested in performing relatively simple outpatient procedures, either in private practice or within the National Health Service. Family doctors, for example, could learn about the basic equipment required as well as the simple techniques of cutaneous surgery (biopsy, curettage, skin suturing, skin grafts and flaps) though, in terms of reconstruction, I would suggest proper supervised training is necessary. For the more ambitious, advice on lasers, dermabrasion, scar revision, chemical face peeling, collagen injection, correction of baldness and facial liposuction is given. These are, of course, more for the private practitioner and more than half of the book is devoted to these cosmetic procedures. This perhaps explains the real reason for the expanding interest of non-plastic surgical specialists in becoming involved in what initially appears to be outside their remit.

Most plastic surgeons would not learn anything new that is not already standard practice or published. They may, however, find the book of interest regarding what other specialties consider they can do. They are likely to dispute the assertion that microscopically controlled tumour excision (Moh's technique) and the method of allowing skin defects to heal by secondary intention are acceptable or totally practical, even if they do work.

The book appears well produced and is illustrated with good-quality diagrams and photographs, some of which are in colour. It is easy to read and not cumbersome to handle. For doctors, of whatever specialty, who might have an interest in the subject of cutaneous facial sugery, it offers interesting and informative reference and can be recommended.

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Computers in Medical Audit. 2nd ed.

M. Rigby, A. McBride and C. Shiels. 240 × 162 mm. Pp. 109. Not illustrated. 1992. London: Royal Society of Medicine. £12·50.

Medical audit is now recognized as an integral and mandatory part of medical practice. The basis of good audit is accurate and timely data collection as part of the normal clinical workload, using appropriate information technology. *Computers in Medical Audit* aims to aid clinicians in making an informed choice of information technology in what is a rapidly expanding and confused market where many have made costly errors.

This short guide was commissioned by the West Midlands Regional Health Authority and is divided into six main sections. It starts with a brief description of the purpose of medical audit and explores the role of computers in this process. However, the heart of the book is its two central sections. The third section consists of a comprehensive review of the facilities offered by the currently available personal computer-based audit systems and is complemented by the results of a user questionnaire. In the fourth section the authors explore the use of mainframe case mix and clinical information systems for medical audit, a new feature in this second edition. The final two sections look at the way data should be structured on hospital computer systems and offers general advice on purchasing considerations within the National Health Service.

I would strongly recommend this clear and concise guide, not only to any hospital clinician who is currently purchasing information technology for medical audit, but also to clinicians whose institutions are assessing case mix and clinical information systems.

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The Immunological Basis of Surgical Science and Practice

O. Eremin and H. Sewell (eds). 240 × 160 mm. Pp. 228. Illustrated. 1992. Oxford: Oxford University Press. £25.

Most surgeons recognize that the success or failure of surgical care rests, in large measure, on factors in the intrinsic make-up of the individual patient. Pre-eminent among these is the immune system, the study of which has undergone an explosive growth that shows no sign of slowing down. This growth in knowledge has outstripped the understanding of most surgical trainees, let alone established surgeons. For some time, therefore, there has been a need for an easily understood textbook that would bring a summary of immunological knowledge and apply it to surgical practice. This is such a book.

The majority of the contributors are British, although there are chapters by authors from Italy and the USA. Most will be well known to the readership of this Journal. The most striking feature of the 200 or so pages of this text is its readability. This is particularly the case with the first and largest chapter, which consists of 70 pages covering basic immunology. This takes the uninitiated through a confusing maze of CD numbers, lymphokines and concepts such as anti-idiotypic networks. The next five chapters consider the five most predictable areas in which immunology is relevant to surgical practice: transplantation, cancer, sepsis, trauma and nutrition. Most of these are again very adequate athough the rapid pace of change in immunology has left some parts of them looking even now out of date. This is most noticeable in the chapter on sepsis in which, for instance, exciting recent advances in cell biology of neutrophil activation in septic shock syndrome are scarcely mentioned.

The following three chapters are perhaps less obvious contributions, but certainly equally worthwhile. These focus on immunotherapy, autoimmune disease and human immunodeficiency virus infection, and the principles of immunological assays and DNA technology. This last chapter is particularly valuable in that it introduces the non-expert to many of the techniques of crucial importance in modern immunology. The last component of the book is an extensive glossary. This is important in that it allows the uninitiated reader to browse and not be brought to an abrupt halt by an unintelligible term.

All books can be criticized. This one certainly has a number of typesetting errors that should have been removed at proof stage. In addition, there are many parts of it with which many immunologists would take issue. This, however, matters little, as it is usually impossible to get any one immunologist to agree with another on anything. It is clearly stated in the preface that this book is written as an introduction to the non-expert surgeon, both trainee and established. I can recommend that both groups purchase this volume.

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Tissue Expansion

G. Magalon, J.-P. Aubert, J. Bardot and P. Paulhe. 255 × 192 mm. Pp. 250. Illustrated. 1992. Marseille: Imprimerie Lamy.

There has been much enthusiasm for tissue expansion over the past decade and this book, part atlas, part cook book, will serve as an excellent guide. It has been produced by a group of plastic surgeons practising in Marseille and is well written and well illustrated with a large number of clear black and white photographs and diagrams.

The text is admirably succinct; there are opening sections on instrumentation and technique that offer clear advice on the choice of expanders, planning, and postoperative management. These are followed by sections on indications for use in the head and neck, breast, trunk and extremities, each concluded by many case reports that carefully detail the size of expanders used, the access incisions, positioning of the valves and timing of the expansion. Explanation of how to make best use of the skin that has been stretched is excellent and there are many useful tips on technique and management. A final chapter surveys complications and how they can be minimized and is again well illustrated. The bibliography is extensive but there are few references within the text.

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A Practical Guide to Head Injury Management

P. V. Marks and C. B. D. Lavy. 180 × 112 mm. Pp. 151. Illustrated. 1992. Philadelphia, Pennsylvania: W. B. Saunders. £9·95.

This book is a concise, practical and easily readable pocket-size manual covering the care of all patients with head injury, from those suffering mild concussion through to those requiring brain stem studies to confirm brain death after severe head trauma. The importance of preventing secondary brain damage as a result of general systemic complications such as hypotension and hypoxia through to intracranial haematomas is stressed throughout the book. Guidelines for admission into hospital and referral to a neurosurgical unit are clearly stated and sufficient statistics are to be found throughout the text to explain the risk factors associated with various clinical and radiological findings and hence the basis on which the guidelines were drawn up. In addition, the book manages to include chapters on the pathological findings of various types of head trauma, the types of complication associated with head injury, the prognosis after injury and a brief surgical section on the techniques used in an emergency situation. There are also chapters on anaesthesia and head injury, and appendices on maxillofacial injuries and the management of children. This book is to be recommended for all medical practitioners and allied staff involved in the day-to-day management of patients with head injury.

P. Chumas

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Notices and announcements

20–21 May 1993
British Association of Endocrine Surgeons
Bristol, UK
Information: Mrs P. Lee, Centre Manager, Edward Jenner Teaching Centre, Bristol Royal Infirmary, Bristol BS2 8HW, UK

28 May 1993
Endovascular Procedures
Bournemouth, UK
Information: Mr S. Parvin, Department of Surgery, The Royal Bournemouth Hospital, Castle Lane East, Bournemouth, Dorset BH7 7DW, UK

2–4 June 1993
International Symposium: Thoracoscopic Sympathectomy
Borås, Sweden
Information: Dr G. Claes, Department of Surgery, Borås Hospital, S-50182 Borås, Sweden

3–5 June 1993
First European Congress of the European Association for Endoscopic Surgery
Cologne, Germany
Information: Medikon-Heide Harzheim, Irmtraud Surmann, PO Box 50 14 70, D-5000 Köln, Germany

7–8 June 1993
8th International Symposium – Applied Physiology in Clinical Respiratory Care
Rotterdam, The Netherlands
Information: Dr O. Prakash, Thorax Centre BD 164, Dijkzigt Hospital, Dr. Molewaterplein 40, 3015 Rotterdam, The Netherlands

8–11 June 1993
World Association of HPB Surgery 1st European Congress of Surgery
Paris, France
Information: EHPBS Congress Secretariat, Congress House, 65 West Drive, Cheam, Surrey SM2 7NB, UK

9–12 June 1993
The Endocrine Society 75th Annual Meeting
Las Vegas, Nevada, USA
Information: Ann Singer, The Endocrine Society, 9650 Rockville Pike, Bethesda, Maryland 20814, USA

4–9 July 1993
Endosurgery – the State of the Art
Hamilton Island, North Queensland, Australia
Information: Kathy Noble, Centre for the Study of Endosurgery, Department of Surgery, Alfred Hospital, Commercial Road, Prahran, Victoria 3181, Australia

5–8 July 1993
First International and Eighth European Conference on Clinical Hemorheology
Vienna, Austria
Information: Professor E. Ernst, Department of Physical and Medical Rehabilitation, University of Vienna, AKH Währinger Gürtel 18–20, 1097 Vienna, Austria

6 July 1993
Current Issues in Epidemiology: the Prevention and Control of Chronic Disease
Cambridge, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

6–17 July 1993
Current Practice in Neonatal and Paediatric Surgery
Manchester, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

8–9 July 1993
Surgical Research Society Meeting
Dundee, UK
Information: Professor J. R. Farndon, Department of Surgery, Bristol Royal Infirmary, Bristol BS2 8HW, UK

8–10 July 1993
XVIIIth International Update on Liver Disease
London, UK
Information: Professor N. McIntyre, University Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

8–10 July 1993
5th South-east European Symposium of Paediatric Surgery
Graz, Austria
Information: Professor M. E. Höllwarth, Department of Paediatric Surgery, University of Graz, Heinrichstraße 31, A-8010 Graz, Austria

6–8 August 1993
First Asian Pacific Congress of Endoscopic Surgery
Singapore
Information: Maggie Phang, Congress Secretariat, Conference and Exhibition Management Services, 09-43 World Trade Centre, Singapore 0409

22–27 August 1993
International Surgical Week – 35th World Congress of the International Society of Surgery
Hong Kong
Information: Congress Secretariat, ISW Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

27–29 August and
30 August to 2 September 1993
Second International Conference of Gastroenterology
Hong Kong and Chengdu, China
Information: Conference Secretariat, Room 1611-13, World Finance Centre, North Tower, Harbour City, Kowloon, Hong Kong

1–3 September 1993
4th International Congress – International Organization for Statistical Studies on Diseases of the Oesophagus
Paris, France
Information: Michele Liegeon, 2 Boulevard de Montparnasse, 75 015 Paris, France

7–10 September 1993
6th International Congress on Interventional Ultrasound
Copenhagen, Denmark
Information: Dr C. Nolsøe, Department of Ultrasound, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark

14–17 September 1993
Eurosurgery '93
London, UK
Information: Professor J. P. S. Lumley, Secretariat, Eurosurgery '93, The Royal College of Surgeons of England, Lincoln's Inn Fields, London WC2A 3PN, UK

15–17 September 1993
Nottingham European Organization for Research and Treatment of Cancer Joint Breast Cancer Meeting
Nottingham, UK
Information: Mrs Wendy Bartram, Professorial Unit of Surgery, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK

29 September to 1 October and
2 October 1993
Principles of Colon and Rectal Surgery, and Biofeedback for Pelvic Floor Disorders/Endorectal Ultrasonography
Minneapolis, Minnesota, USA
Information: Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue South-east, Minneapolis, Minnesota 55414, USA

17–23 October 1993
Surgery of the Liver, Biliary System and Pancreas
Edinburgh, UK
Information: Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

10–13 November 1993
CA-125 Ten Years Later: Biology and Clinical Applications – Present and Future
San Remo, Italy
Information: MAF Servizi, Via Vico 7, 10128 Turin, Italy

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References: **1.** Bergqvist D. Post-operative thromboembolism. Frequency, etiology, prophylaxis. Berlin: Springer-Verlag, 1983. **2.** Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal p
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